AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION
FOR THE STUDY OF THE CIRCULATION

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Contents on Inside Cover

American Heart Journal

CONTENTS FOR JANUARY, 1954

Original Communications

	Page
A Study of the Physical Properties of the Ballistocardiograph. John L. Nickerson, Ph.D., and James A. L. Mathers, M.D., New York, N. Y.	1
Ballistic Respiratory Variation as Measured by the Electromagnetic Ballistocardiograph. William H. Anderson, M.D., Karl Urbach, M.D., and Alexander A. Doerner, M.D., Staten Island, N. Y.	15
The Effects of Cigarette Smoking on the Ballistocardiograms of High School Youths. J. J. Kelly, Jr., M.D., A. Caccese, M.D., J. Ortiz-Marquez, M.D., and F. Taubman, M.D., New York, N. Y.	30
Ballistoscope Recording With the Aid of an Asymmetrical Shutter. Samuel Losner, M.D., Brooklyn, N. Y.	34
Value of Additional Thoracic and Abdominal Unipolar Leads for Diagnosis of the Location and Extension of Myocardial Infarctions. Joseph Lambert, M.D., Spa, Belgium	40
Functional Anatomy and "Throttle Valve" Action of the Pulmonary Veins. G. E. Burch, M.D., and R. B. Romney, M.D., New Orleans, La.	58
Studies on Whole Blood and Muscle Creatine Levels: Effect of Systemic and Local Anoxia, of Cardiac Failure and Compensation, and of Alpha-tocopherol Administration. Don C. Sutton, M.D., George C. Sutton, M.D., George F. Hinkens, M.D., William B. Buckingham, M.D., and Raymond Rondinelli, B.S., Chicago, Ill.	67
Certain Cardiovascular Effects of Vasopressin (Pitressin). Khalil G. Wakim, M.D., Clarence Denton, M.D., and Hiram E. Essex, Ph.D., Rochester, Minn.	77
Analeptic Effects of Aranthol in Vasomotor Depression Induced by Quinidine. S. A. Weisman, M.D., S. J. Weisman, M.D., and E. J. Prescott, B.S., Los Angeles, Calif.	84
A Line-Operated Direct-Coupled Electrocardiograph. P. Sekelj, D. Eng., L. A. Geddes, M. Eng., and H. E. Hoff, M.D., Houston, Texas	95
An Improved Flarimeter. Philip V. Wells, D.Sc., Newark, N. J.	102

Clinical Reports

Pulmonary Artery Thrombosis Simulating Pulmonic Valve Stenosis With Patent Foramen Ovale. E. Grey Dimond, M.D., and T. Reid Jones, M.D., Kansas City, Kan.	105
Acute Myocardial Infarction Associated With Acute Porphyria. Louis F. Albright, M.D., F.A.C.P., and Frank J. Brown, M.D., Point Pleasant, N. J.	108
Right Ventricular Stenosis of the Bernheim Type in a Case of Septal Infarction. Arsénio Cordeiro, M.D., Lisbon, Portugal	112
Acute Isolated Myocarditis Simulating Coronary Occlusion. J. G. Gillis, M.D., and M. B. Walters, M.D., F.R.C.P. (C), Vancouver, Canada	117

Critique

The Theoretical and Experimental Bases of the Frontal Plane Ventricular Gradient and Its Spatial Counterpart. Ernst Simonson, M.D., Otto H. Schmitt, Ph.D., James Dahl, M.D., Donald Fry, M.D., and Earl E. Bakken, B.E.E., Minneapolis, Minn.	122

Book Reviews

Book Reviews	154

Announcements

Announcements	157

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American Heart Journal

VOL. 47 JANUARY, 1954 NO. 1

Original Communications

A STUDY OF THE PHYSICAL PROPERTIES OF THE BALLISTOCARDIOGRAPH

JOHN L. NICKERSON, PH.D.,* AND JAMES A. L. MATHERS, M.D.

NEW YORK, N. Y.

THE function of the ballistocardiograph is to detect and record the impulses produced by the changes in motion of the blood in the heart and vascular tree. Since the original impulses are transmitted through the body and recorded as movements of a ballistic system, it is likely that distortion may be present in the record. That such distortion occurs has been reported by Nickerson and Mathers[1] who showed that the form of the ballistocardiogram depends on the ballistocardiograph with which the record is made. It is the purpose of the present study to investigate the physical properties of the body and of the ballistic bed in order to determine the quality of the various ballistocardiographs in present use.

THEORY

A sinusoidal force component of frequency n arising at the heart is transmitted outward through the body. This component may undergo in transmission an amplitude distortion (Ta) and a phase shift (T_θ). On arriving at the ballistic bed this altered component of the original impulse may again suffer distortion in amplitude (Ra) and a shift of phase (R_θ). If the recording system records the movements of the ballistic bed in a precise manner then the total amplitude

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distortion is given by the product Ta × Ra and the complete phase shift by the sum $T_\theta + R_\theta$. Furthermore, if the body and bed are simple oscillators the formulas for these distortions may be obtained from purely mechanical considerations[2] and are as follows:

$$Ta = \frac{\sqrt{1 + (2\gamma_1 n/N_1)^2}}{\sqrt{(1 - n^2/N_1^2)^2 + (2\gamma_1 n/N_1)^2}}$$

$$Ra = \frac{1}{\sqrt{(1 - n^2/N_2^2)^2 + (2\gamma_2 n/N_2)^2}}$$

$$T_\theta = 180^\circ + \tan^{-1} \frac{2\gamma_1 (n/N_1)^3}{1 - (n/N_1)^2 + (2\gamma_1 n/N_1)^2}$$

$$R_\theta = \tan^{-1} \frac{2\gamma_2 n/N_2}{1 - (n/N_2)^2}$$

where n is the impressed frequency, N_1 is the natural frequency of the body, γ_1, its damping as a fraction of critical damping, N_2, the natural frequency of the ballistic bed and γ_2, its damping as a fraction of critical damping.

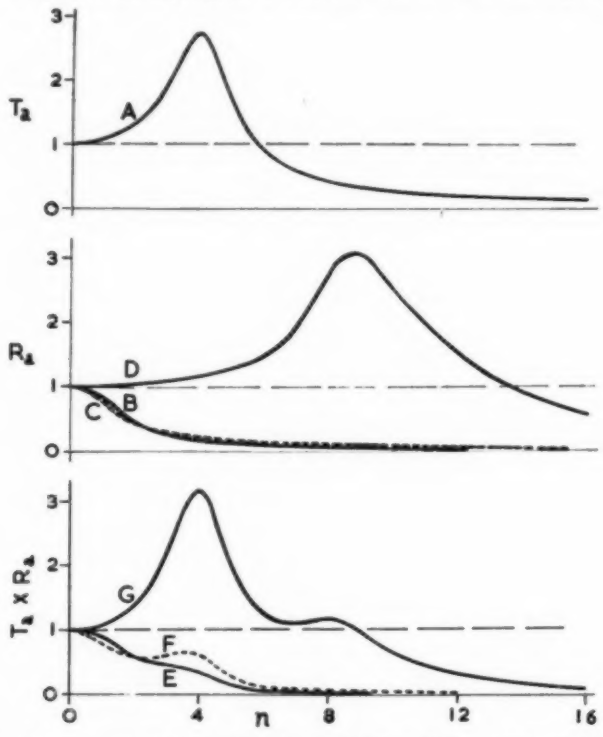

Fig. 1.—Curve *A* represents the transmission distortion factor (*Ta*) which alters a sinusoidal oscillation of frequency *n* passing through a body of natural frequency $N_1 = 4$ cycles per second and of damping value $\gamma_1 = 0.2$. Curves *B*, *C*, and *D* represent the distortion factor (*Ra*) arising in the response of the ballistic bed to a sinusoidal signal, for, respectively, the low-frequency system ($N_2 = 1\frac{1}{2}$, $\gamma_2 = 0.85$), the same system considering the unloaded bed only ($N_2 = 3$, $\gamma_2 = 1.70$) and the high-frequency system ($N_2 = 10$, $\gamma_2 = 0.2$). Curves *E*, *F*, and *G* represent the resultant distortion arising from the combination of curve *A* in turn with curves *B*, *C*, and *D*.

The damping factor γ is determined by the equation

$$\gamma = \log_e X_1/X_2/\sqrt{4\pi^2 + (\log_2 X_1/X_2)^2}$$

where X_1 and X_2 are the amplitudes of successive waves in the decreasing sequence obtained when the body or bed is set in oscillation by a single impact.

The manner in which the transmission amplitude factor affects an impulse is demonstrated by Fig. 1, curve *A*. It can be seen that transmission through the body causes considerable distortion, e.g., the amplitude of a four cycle component is accentuated 2.7 times whereas a 10 cycle component is reduced to one-quarter of its incident magnitude.

The effect of the response of the ballistic system on the transmitted signal depends on the form of the response curve. A high frequency underdamped system, illustrated in Fig. 1, curve *D*, further accentuates the components of frequencies around 4 cycles per second as shown by the resultant, Fig. 1, curve *G*. For the low frequency critically damped system the combined distortion by transmission and response is shown by Fig. 1, curve *F*. There is minor distortion in the range 1 to 4 cycles but from 5 cycles upward the contributions of the components of higher frequency are progressively diminished.

The manner in which the phase angles of the various components are affected by the transmission through the body and by the response of the ballistic bed are shown in Fig. 2. Curve *G* illustrates the result for the high frequency system and curve *F* for the low frequency critically damped system. An ideal undistorted response would be indicated by a linear relationship between phase lag and frequency. Since neither curve is a straight line neither system is ideal.

Direct ballistocardiographs in which no bed is used require only a consideration of the response factors Ra and R_θ provided that the pickup system does not act as an oscillator of frequency characteristics which will introduce distortion into the record. The distortions produced by these factors in a body of natural frequency $N_2 = 4$ cycles per second and $\gamma_2 = 0.2$ are illustrated in Fig. 3. In this situation the 3½ cycle component is accentuated three times and the 10 cycle component reduced to one-fifth of its initial value. It is to be noted also that the phase shift is not linear with frequency over the full range.

METHOD

Seven subjects whose ages range from 18 to 79 years have been studied in this investigation. One of these individuals had a coarctation of the aorta. The other six subjects were classified as healthy on the basis of history, physical examination, electrocardiogram and two-meter roentgenograms of the chest.

Displacement ballistocardiograms of each of these subjects in the resting state were recorded with four different ballistic systems. These systems were, respectively, *1*, the low-frequency, critically damped system[3]; *2*, a middle-frequency partly damped system; *3*, a high-frequency partly damped system[4]; and *4*, a direct ballistocardiograph where the body alone is the oscillating system.[5] The exact values of frequency and damping for each ballistocardiograph and the characteristics for each subject are presented in Table I.

TABLE I

SUBJECT				BODY FREQUENCY DAMPING			BALLISTOCARDIOGRAPH							
							LOW FREQUENCY CRITICAL DAMPING		MIDDLE FREQUENCY		HIGH FREQUENCY		DIRECT	
NO.	SEX	AGE	CARDIAC STATUS	N_1	T_1		N_2	T_2	N_2	T_2	N_2	T_2	N_2	T_2
1	M	48	Healthy	4.1	0.25	A	1.5	0.86	2.0	0.40	7.2	0.055	4.1	0.25
						B	2.9	1.67	3.9	0.78	9.5	0.072		
2	M	38	Healthy	4.0	0.20	A	1.5	0.86	2.0	0.40	7.2	0.055	4.0	0.20
						B	3.0	1.72	4.0	0.80	10.0	0.076		
3	M	28	Healthy	4.1	0.23	A	1.5	0.86	2.0	0.40	7.2	0.055	4.1	0.23
						B	2.8	1.61	3.7	0.74	9.1	0.070		
4	M	79	Healthy	4.5	0.20	A	1.5	0.86	2.0	0.40	7.2	0.055	4.5	0.20
						B	2.8	1.61	3.7	0.74	9.1	0.070		
5	M	37	Healthy	4.1	0.22	A	1.5	0.86	2.0	0.40	7.2	0.055	4.1	0.22
						B	2.8	1.61	3.7	0.74	9.1	0.070		
6	F	27	Healthy	4.0	0.16	A	1.5	0.86	2.0	0.40	7.2	0.055	4.0	0.16
						B	2.7	1.55	3.6	0.72	8.8	0.067		
7	F	18	Coarctation of aorta	4.2	0.25	A	1.5	0.90	2.0	0.50	7.0	0.083	4.2	0.25
						B	2.7	1.55	3.6	0.72	8.8	0.101		

A = Totally loaded ballistocardiograph; B = Unloaded ballistocardiograph.

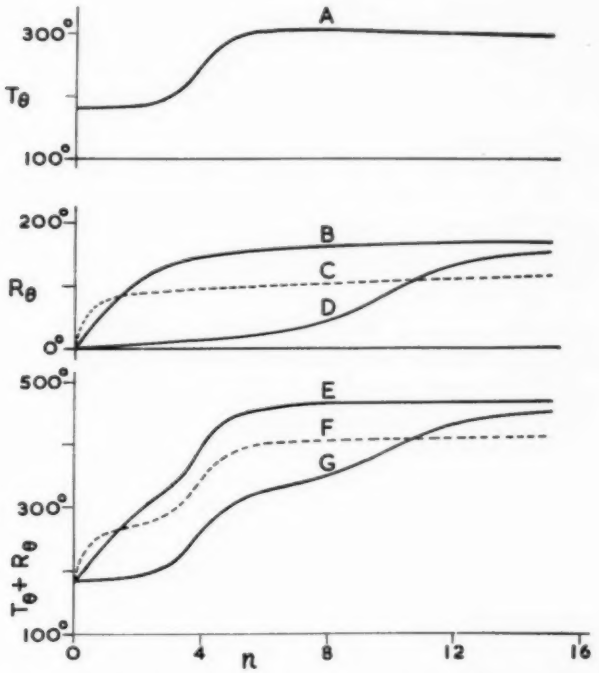

Fig. 2.—Curve *A* represents the phase lag (T_θ) appearing when a sinusoidal oscillation of frequency *n* is transmitted through a body of natural frequency $N_1 = 4$ and damping $\gamma_1 = 0.2$. Curves *B*, *C*, and *D* represent the phase lag (R_θ) appearing when the responding ballistic bed is, respectively, a low-frequency system ($N_2 = 1.5$, $\gamma_2 = 0.85$), the same system considering the unloaded bed only ($N_2 = 3.0$, $\gamma_2 = 1.70$) and the high frequency system ($N_2 = 10$, $\gamma_2 = 0.2$). Curves *E*, *F*, and *G* represent the total phase lag arising from the combination of curve *A* in turn with curves *B*, *C*, and *D*.

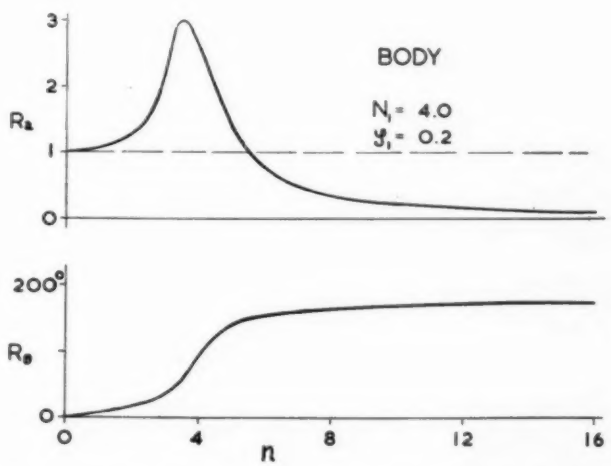

Fig. 3.—This figure presents curves representing the body response distortion in amplitude, *Ra*, and shift in phase R_θ for a body with natural frequency $N_2 = 4$ and $\gamma_2 = 0.2$.

Each of the twenty-eight ballistocardiograms obtained was submitted to a Fourier harmonic analysis to fifteen terms on I.B.M. computing machines. The Fourier coefficients were corrected for body transmission distortion Ta (experimental value) and T_θ and for ballistocardiographic response distortion Ra and R_θ. These corrected Fourier coefficients represent the undistorted acceleration (or force) components giving rise to the ballistocardiogram. Integration of these Fourier Series in two stages produces successively the undistorted velocity and the undistorted displacement series.

The body frequency and damping factors recorded in Table I were determined by recording the movements of the body subsequent to tapping the head or to displacing the body from its resting position by a push against head, shoulders, or hips—the subject lying upon a rigid desk or table top. The recordings of these movements were generally made from the instep but for purposes of comparison were taken occasionally from a block mounted on the shins or from the head.

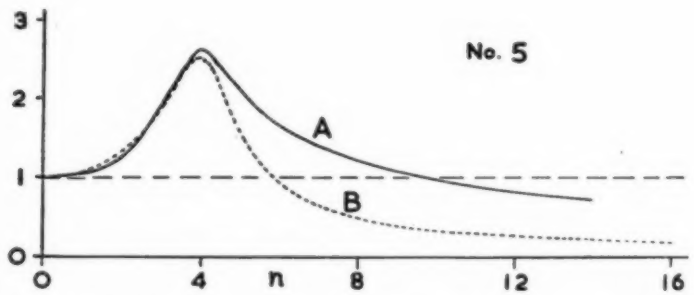

Fig. 4.—Curve *A* presents for subject No. 5 the experimental transmission distortion factor Ta determined by use of the mechanical oscillator. Curve *B* presents for the same subject the theoretical distortion factor based on a single body frequency of value $N_1 = 4.1$ with damping $\gamma_1 = 0.22$.

These frequency and damping values were checked by another method.[6] A ballistic bed was arranged so that its response characteristics were known. The subject lay upon the bed with a mechanical rotating oscillator placed upon the lower chest and upper abdominal region. The rotating oscillator produced sinusoidal forces along the long axis of the system with frequencies between 0 and 15 cycles per second. The magnitude of these forces was given by $4\pi^2MKn^2/g$ grams where K is the radius of gyration of the mass M rotating at a frequency n per second. The zero frequency response was determined by displacing the system with a steady force. Since the impressed force components and the response characteristics of the bed were known and since the resultant response of the bed was recorded it was possible to determine the transmission characteristics of the body. The results were in reasonable agreement with the values obtained by the previous method. The agreement is illustrated in Fig. 4.

Two important considerations required clarification at this stage. The first: Does an impulse arising in the heart follow a pathway mechanically equivalent to that followed by an impulse applied to the chest and abdomen? To answer this question the ballistocardiograph was arranged to have a natural frequency of four cycles per second and a damping factor much below the critical value. In this situation the impulses from the heart produced an almost steady sinusoidal oscillation, Fig. 5, so that the record in no way resembled the normal ballistocardiogram. This observation is evidence of resonance and it suggests that the body characteristics determined by the methods discussed here provide a reasonable description of the transmission from the heart to the ballistic bed.

The second point to consider is whether there are other significant natural oscillation frequencies in the body. The curves in Fig. 4 show a difference between the theoretical transmission curve *B* which was based on a single oscillation frequency and the experimental transmission curve *A*. Since curve *A* lies above curve *B* at higher frequencies there exist therefore body frequency components above four cycles per second. Such higher frequency components can be elicited by tapping the head sharply. The high frequency indicates a degree of tenseness in the oscillating structure which suggests that the oscillation arises in the skeletal parts such as the spinal column.

RESULTS

Representative ballistocardiograms made with the four types of instruments on the seven subjects are shown in Figs. 6 and 7.

Reconstruction of the patterns from the Fourier coefficients obtained by harmonic analysis demonstrated, as in Fig. 8, excellent agreement with the original pattern when the analysis was carried to fifteen terms and fair agreement when carried to six terms.

The differences in pattern obtained when records are made on the same subject by the various ballistocardiographs are obvious in Figs. 6 and 7. These differences are demonstrated quite as remarkably when the coefficients of the Fourier expansions are compared. This comparison is shown in Fig. 9 where the lines indicated as *L*, *M*, *H* and *B* represent by their lengths the relative values of the coefficients for subject No. 7 for each frequency component obtained from the four types of ballistocardiograph.

Correction of these coefficients for distortion using the experimental value of Ta, as in curve *A*, Fig. 4, and correction for the distortion by the ballistic bed response Ra produce from the original four sets of Fourier coefficients four sets of corrected coefficients which are in fair agreement and can be considered the coefficients of a basic Fourier series describing the forces (or accelerations) arising at the heart.

The agreement among these four sets of corrected coefficients is illustrated in Fig. 10. In this figure are plotted the standard deviation from the mean of each set of four corresponding coefficients for the corrected and for the uncorrected series. In all cases the standard deviation from the mean has been reduced by the corrections applied. This reduction of the standard deviation can be taken

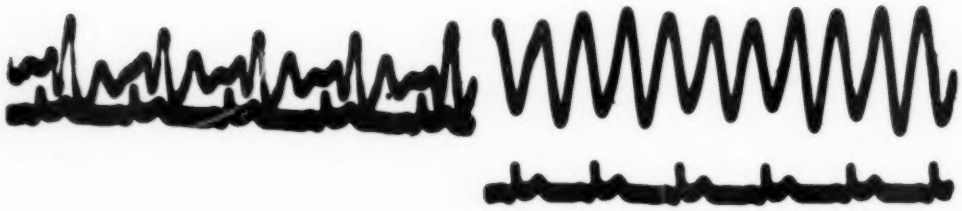

Fig. 5.—The curve on the left shows the normal low frequency, critically damped ballistocardiogram. The curve on the right shows the resonance effect appearing when the ballistocardiograph has low damping and a natural frequency close to that of the equivalent transmission frequency of the body.

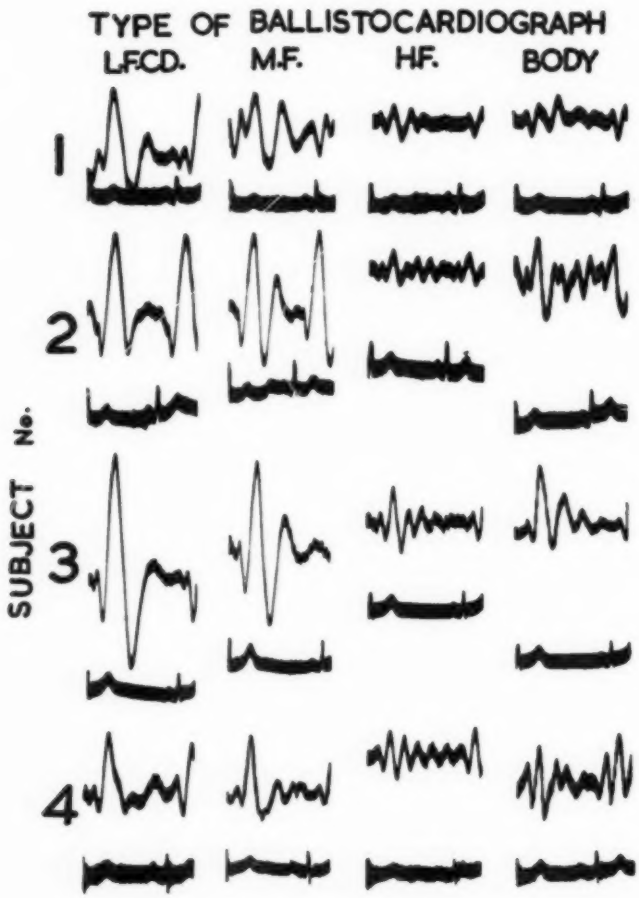

Fig. 6.—The four types of ballistocardiograms on subjects *1*, *2*, *3*, and *4*.

to indicate that the corrections have acted to converge the four sets of coefficients toward a common basic set. Such agreement indicates that although the original analyses were quite different the application of the appropriate corrections for transmission and response lead toward a common basic pattern. The extent of this agreement is quite remarkable since the records analyzed were selected at random and by the nature of the investigation could not have been recorded simultaneously. Distortion introduced by the pickup of the direct ballistocardiograph has been ignored in these computations. Preliminary estimates indicate that correction for this distortion would further improve the correlations between the corrected coefficients for the four different ballistocardiographs.

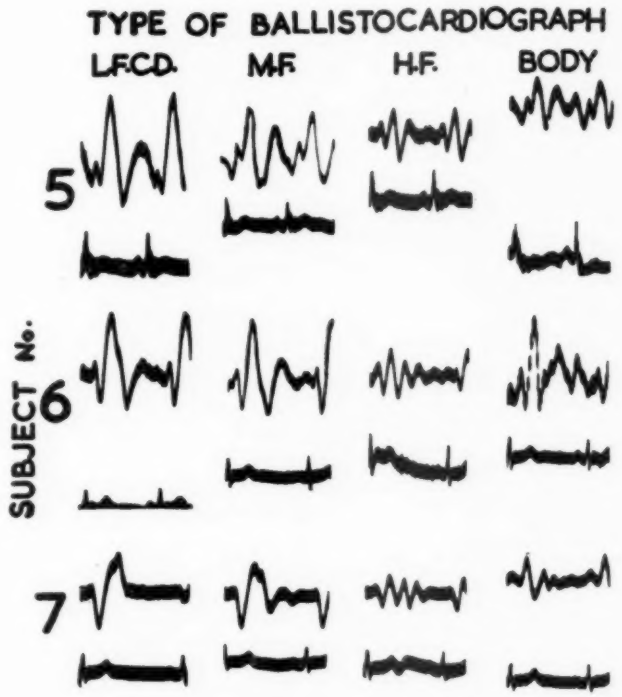

Fig. 7.—The four types of ballistocardiograms on subjects *5*, *6*, and *7*.

The coefficients of the Fourier series representing this basic acceleration pattern are illustrated in Fig. 11 by the heavy lines designated as *A*. These coefficients are the mean values of the corrected coefficients. Integration of this basic acceleration series produces a set of coefficients designated by *V* in Fig. 11 and representing a basic velocity series. Another stage of integration produces a set of coefficients designated by *D* in Fig. 11 and representing a basic displacement series.

It is significant that the basic series for acceleration, velocity and displacement need in general to be carried only to 11, 7, and 4 terms, respectively, for satisfactory representation.

Since the actually recorded patterns from all types of ballistocardiographs have some distortion from the basic pattern it is important to determine the degree of this distortion. Examination of Fig. 11 permits the comparison of the coefficients from the four types of ballistocardiograph with the basic patterns for acceleration, velocity, and displacement. Some degree of correlation is apparent.

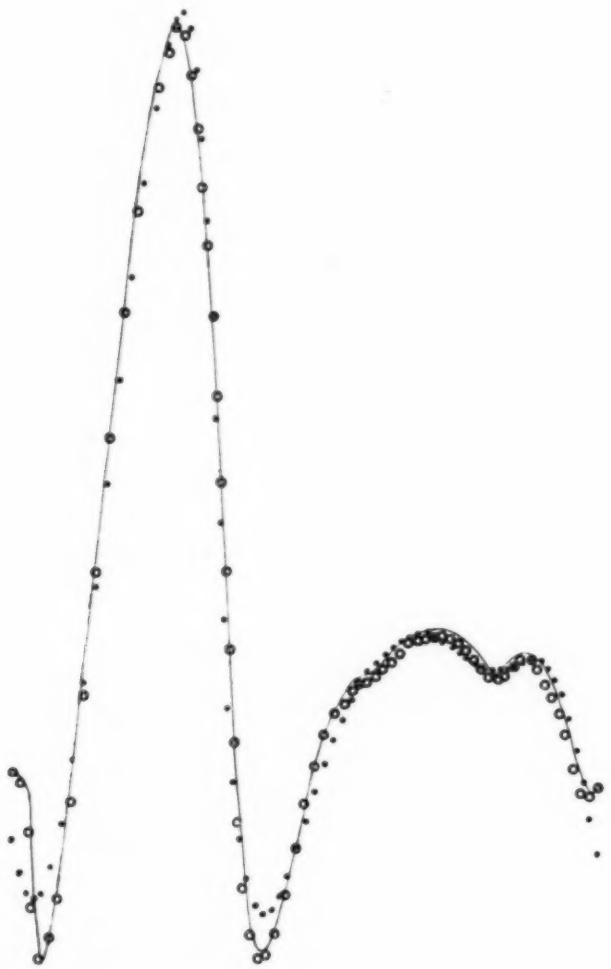

Fig. 8.—The solid curve represents an original ballistocardiogram. The circles represent the reconstruction of this curve from the Fourier analysis to 15 terms and the dots the reconstruction from the first 6 terms of this analysis.

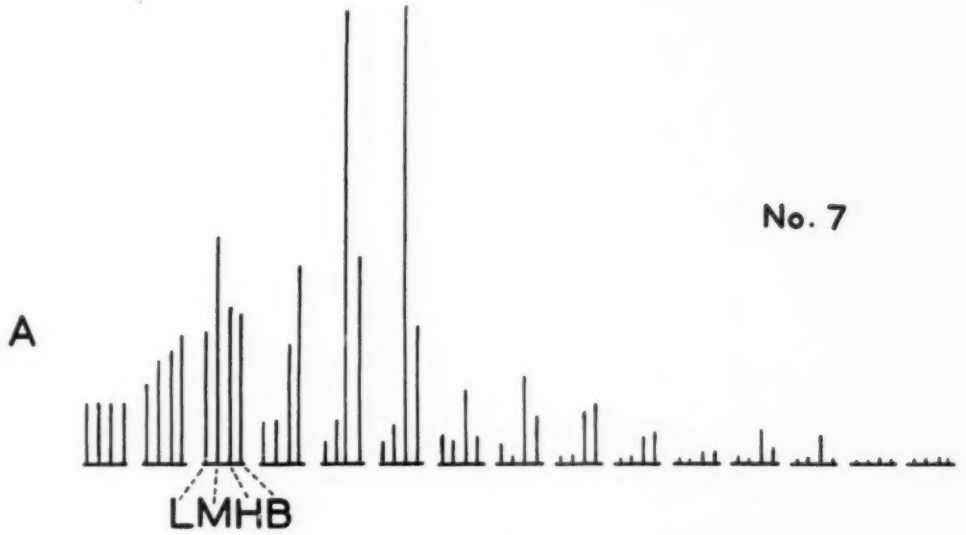

Fig. 9.—This figure illustrates for subject No. 7 the relative values of the Fourier coefficients of the four different ballistocardiograms for each value of n from 1 to 15. As lettered for the component for which n equals 3 each corresponding line of each group represents in that order the value of the coefficient for L = the low frequency, critically damped ballistocardiograph, M, the middle frequency ballistocardiograph, H, the high frequency ballistocardiograph, and B = the direct ballistocardiograph.

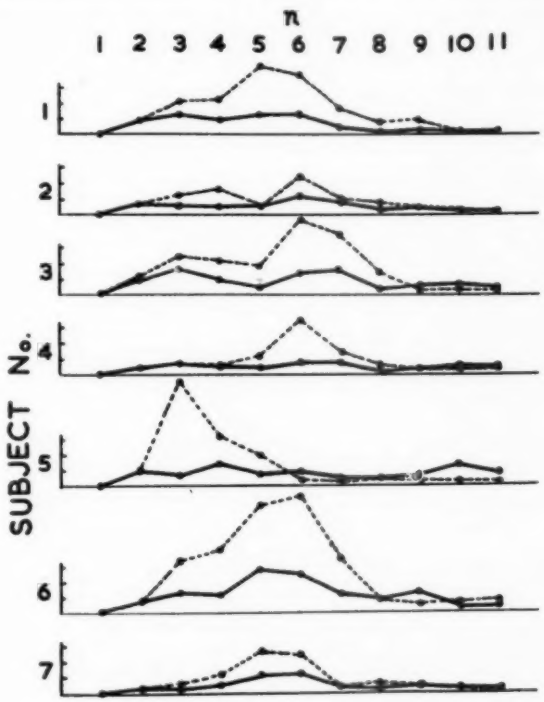

Fig. 10.—This figure presents the values of the standard deviation between the Fourier coefficients of the four types of ballistocardiograms for each term of the analysis carried to eleven terms. The points connected by the dotted lines are from the original analyses of the ballistocardiogram whereas the points connected by the solid lines are from the analyses corrected for transmission and ballistic response distortion. The effect of these corrections is to reduce the standard deviation, i.e., to bring the four resultant Fourier series into closer agreement than was found in the four original analyses.

The best correlation of all the systems studied (r = 0.900; S.D., 0.076; range, 0.731 to 0.970) is between the low frequency, critically damped ballistocardiograph and the basic velocity pattern. The high frequency system has its best correlation (r = 0.718; S. D., 0.084; range, 0.551 to 0.833) with the basic acceleration pattern. The best correlation of the direct ballistocardiograph (r = 0.562, S. D., 0.206; range, 0.194 to 0.777) is with the basic acceleration pattern.

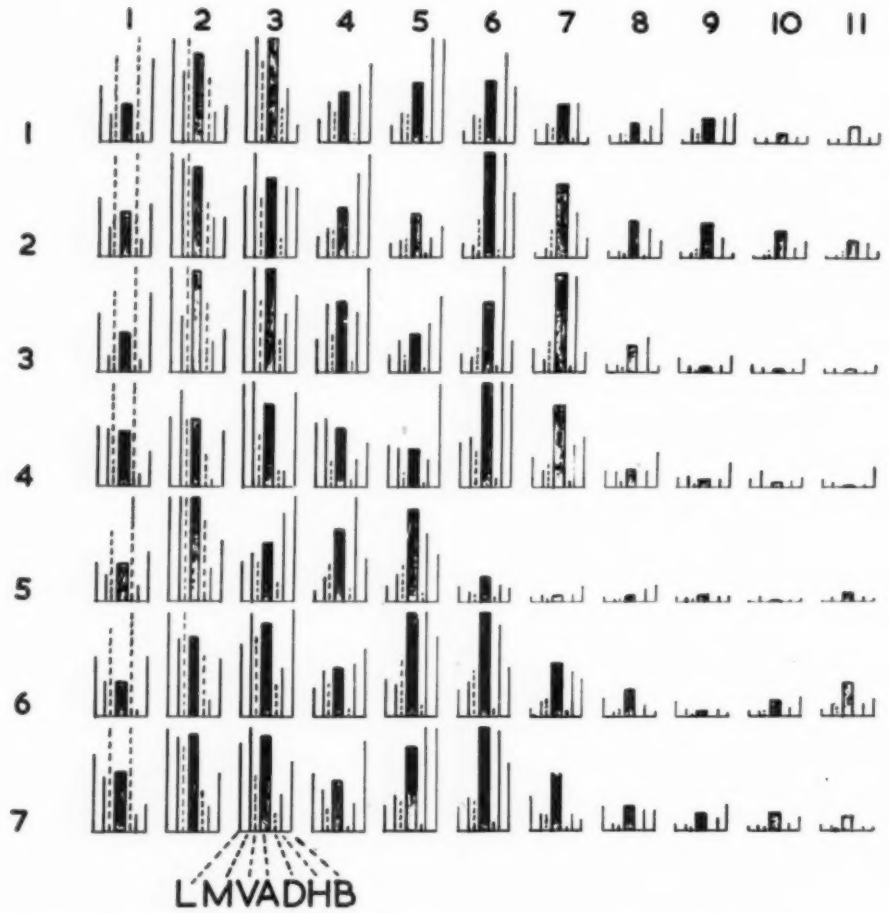

Fig. 11.—This figure represents a summary of all Fourier analyses carried to eleven terms for the seven subjects on the four ballistocardiograms, as well as the three basic functions derived by correcting the original analyses for transmission and response distortion. As illustrated by the third term for subject No. 7 these lines represent by their lengths the values of coefficients, for successively:

L, the low frequency critically damped ballistocardiograph; *M*, the middle frequency ballistocardiograph; *V*, the basic corrected velocity pattern; *A*, the basic corrected acceleration pattern; *D*, the basic corrected displacement pattern; *H*, the high frequency ballistocardiograph; *B*, the direct ballistocardiograph.

DISCUSSION

The research presented in this paper has developed the view suggested by one of the authors in an earlier paper[7] that the ballistocardiograph should be considered as a system of coupled oscillators rather than as a single oscillating system. The separation of body and bed as two coupled oscillators has been attempted. This separation can be considered as occurring at either of two levels: A, when the transmission characteristics of the body are considered to be acting upon the totally loaded system of body and bed, or, B, when these characteristics are considered to be acting between the body and the bed, i.e., upon the unloaded bed. The designations A and B in Table I demonstrate the corresponding response characteristics under these two conditions. In the present investigation the results reported are based on the more exact considerations of method B. However, over most of the frequency range of importance the response difference between these two approaches is not great. This is illustrated by curves *E* and *F* of Fig. 1. This degree of agreement is important since it gives support to earlier work based on the simpler considerations of the totally loaded single oscillator and is a point of particular importance for the low frequency critically damped ballistocardiograph in which the adjustment for frequency and damping has been based on the totally loaded condition.

The assumption that the transmission distortions produced in the body can be lumped together and attributed to a single oscillation frequency with its appropriate damping is obviously an oversimplification. However, the computation of the corrections from the experimental rather than from the theoretical transmission curves is an attempt to improve the correction for distortion arising in transmission.

The determination of the acceleration (or force) components in the basic ballistocardiogram has not been attempted previously. The frequency analysis given by Braunstein and associates[8] is an analysis of the high-frequency ballistocardiogram uncorrected for distortions introduced by the body.

The results of the present work indicate that frequency components up to eleven cycles per second are important in the formation of the acceleration pattern. However, no ballistocardiograph in current use corrects adequately for the distortion introduced by the body into the acceleration pattern.

The basic velocity pattern is reasonably well represented by frequency components up to 8 cycles per second. The instrument which most nearly produces this pattern is the low frequency, critically damped system. However, even in this case there is some phase distortion in the components above six cycles per second.

No system produces in a satisfactory manner the corrected basic displacement pattern.

SUMMARY

Fourier analyses of the displacement ballistocardiograms of seven subjects recorded from four types of instruments have been made. The coefficients of these series were corrected for the distortion introduced by the ballistic bed and by transmission through the body. The coefficients representing the ballistic pattern from the four instruments were for each subject quite different in value in the corresponding terms. The effect of applying the corrections was to converge the coefficients of the corresponding terms of the series toward a common value. The common pattern thus predicted represents a basic acceleration pattern (or forcing function) and, by appropriate steps of integration, the associated velocity and displacement patterns.

The coefficients of these basic series were compared with those of the original series obtained from the analyses of the patterns from the various instruments. This comparison was made in order to determine how closely the basic patterns are approximated by the records made by these instruments. The best agreement is between the pattern obtained from the low-frequency, critically damped ballistocardiograph and the basic velocity pattern. The next best correlation was between the high-frequency underdamped system and the basic acceleration pattern.

It is also suggested from this research that the acceleration, velocity, and displacement can be represented with sufficient accuracy by Fourier series carried out to 11, 7, and 4 terms, respectively. This finding indicates, for example, that a ballistocardiograph adequate to represent the acceleration pattern must have a frequency response which is linear to 11 cycles per second and that adequate mechanical or electrical filtering must be present to eliminate the distortion introduced by the transmission of impulses through the body.

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BALLISTIC RESPIRATORY VARIATION AS MEASURED BY THE ELECTROMAGNETIC BALLISTOCARDIOGRAPH

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THE primary systolic waves of the ballistocardiogram are labelled H, I, J, and K. The respiratory variation in amplitude between inspiratory IJ and expiratory IJ which is frequently seen in the presence of coronary artery disease and the definition of the normal limit were reported by Brown and associates.[1-3] These workers used a Starr bed ballistocardiograph and defined the respiratory variation in terms of an index calculated by determining the ratio of expiratory minute volume to inspiratory minute volume. Brown and associates[3] have subsequently stated that it should be possible to set up normal standards using the ratio of the absolute amplitudes of the inspiratory and expiratory IJ and felt that when the amplitude of the expiratory IJ was one-half or less than the inspiratory, that the respiratory variation was abnormal.

It appears that the size of the I and J waves is related to the force of cardiac ejection, and the form of the ballistic curve is determined by the curve of ejection velocity.[4,5] In general, large I and J waves indicate high velocity and high stroke volume, small I and J indicate decreased velocity and small ejection volume.[6] However, Brant and associates[7] have shown that regardless of the type of ballistocardiograph employed, the administration of nitroglycerin is followed by an increase in the amplitude of IJ but a decrease in diastolic size of the heart and in stroke volume. It, therefore, appears that the ballistic curve, regardless of the method of recording, is greatly influenced by velocity of cardiac ejection and blood flow in the great vessels. With this fact in mind our study was conducted with an instrument designed to reflect velocity changes, that is the electromagnetic ballistocardiograph. This instrument also has the advantage of simplicity and adaptability for office and general hospital use.

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No study comparable to that of Brown and associates[1] has been carried out utilizing the portable ballistocardiograph. It has been stated for both the electromagnetic and photoelectric instruments that expiratory IJ may normally be as small as 60 per cent of the inspiratory IJ, $\frac{\text{Inspiratory IJ}}{\text{Expiratory IJ}}$ of $\frac{100}{60}$ or 1.6.[8,9] Rubenstein[10] noted that an expiratory decrease of approximately 50 per cent may be seen in the amplitude of IJ.

There appeared to be no clear-cut definition of the normal limit of respiratory variation to be expected with the electromagnetic ballistocardiograph, and the range of respiratory variation with disease states had not been delineated. The present study was undertaken, therefore, in an attempt to define the normal limit of ballistic respiratory variation and to call attention to the magnitude and frequency of this variation in disease states.

MATERIAL

Most of the patient material for this study was derived from the wards of the medical service of the United States Public Health Service Hospital, Staten Island, New York. A few were ambulant patients referred from the outpatient department and a few were physicians or other hospital personnel. All were men.

Normal Persons.—This group consisted of seventy-nine individuals, many were convalescent in the Gastrointestinal Service at the time they were studied. Their ages ranged from 16 to 59 years with a mean of 35 years for the group. The criteria for normality were: (a) freedom from signs or symptoms referable to the cardiovascular system, (b) a normal 12-lead electrocardiogram and in most instances a normal standard exercise test,[15] (c) cardiac size within normal limits as shown by routine chest roentgenogram.

Hypertensive Patients.—Thirty-nine subjects with a sustained blood pressure of 160/100 mm. Hg or greater were included in this group. The youngest was 29 years, the eldest 71 years. The mean age for the group was 50 years. The majority had left ventricular enlargement by roentgenogram and/or electrocardiogram.

Coronary Artery Disease.—There were sixty-seven patients in this group. They ranged in age from 34 to 78 years, with a mean of 56 years. Each of these patients had one or more of the following: (a) evidence of a previous myocardial infarction, (b) a positive two-step standard exercise test, (c) a history of a crushing type of precordial pain radiating into the neck and/or arms, occurring with exercise and relieved by nitroglycerine, or (d) abnormal T waves electrocardiographically without any demonstrable cause but with congestive failure at some time. Group (d) was in the minority. (Two patients who had bundle branch block only are included in the coronary disease group.)

Emphysema.—Of thirty-one patients in this group three had undergone pneumonectomy some months previously and were therefore comparable to the remainder of the group in that they had a decrease in the pulmonary vascular pool. The diagnosis of emphysema was made by clinical and roentgenographic methods. This group had an average age of 52 years with a low of 38 and a high of 68 years.

There was a fifth heterogeneous group of twelve individuals with two or more of the diseases under study. This group varied in age from 45 to 72 years with a mean age of 56 years. Although this group is not large enough to enable one to arrive at statistical conclusions, it is included for completeness and because the question naturally will arise concerning the appearance of the ballistocardiogram in the presence of both coronary artery disease and emphysema.

METHOD

The ballistocardiograms were recorded on a Sanborn Viso-Cardiette by means of an electromagnetic instrument built to the specifications of Dock and associates[8,11] with one modification. The magnet was placed on the board across the ankles, and the coils were held on a stationary stand between the ankles. The magnet passed back and forth between the coils with each movement of the body in the longitudinal plane. This was done to remove any impeding effect the lead wires might have if the coils were attached to the ankle board as in the original instructions of Dock. Records obtained by both means are quite comparable so long as care is taken to allow sufficient slack in the lead wires leading to the coils when attached to the ankle board. A 20-microfarad condenser was used to filter out the low-frequency respiratory movements of the diaphragm.

The tests were conducted after the patient had been lying on a metal-topped table for at least ten minutes, at least fifteen minutes after smoking,[12,13] and at least one hour after the last meal.[14] For purposes of this study, all ballistocardiograms were recorded during normal respiration. Standard 12-lead electrocardiograms were usually recorded just prior to the ballistocardiogram.

Prior to the analysis of all records in each group, a small pilot study was done. The ballistocardiograms of eleven in the normal group, eleven of the hypertensive group, twelve of the coronary artery disease group and ten patients of the emphysema group were completely analyzed for the respiratory variation in amplitude of each systolic wave (H, I, J, K), as well as for the amplitude of IJ in particular. These records were chosen at random, and amplitude measured in millimeters. The respiratory ratio was determined by first selecting two typical inspiratory complexes and two typical and repeatable expiratory complexes. A base line was established and the amplitude of each wave from the base line was determined in each of the selected complexes. The inspiratory and expiratory value used for the calculation of the ratio was the mean of the particular two inspiratory or expiratory complexes analyzed. Several patients were excluded from each of the large groups of diseased patients because their ballistic complexes could not be identified. This necessitated the exclusion of all patients with a Grade 4 ballistocardiogram and several with a Grade 3 record.

RESULTS

The results of this pilot study are given in Fig. 1. It appeared from this preliminary analysis that the respiratory variation of the H and K waves, respectively, was useless as a means of indicating ballistic abnormalities; even though the coronary artery disease and emphysema groups did have a greater ratio of the H wave than that of the normal group or hypertensive patients. Those with emphysema had a very large respiratory ratio of the I wave, and the coronary artery disease group had the largest ratio when comparing the J wave. However, when the IJ strokes were compared for respiratory ratio it was noted that the normal group averaged 1.5; the hypertensive group, 1.9; the coronary artery disease patients, 2.1; and the emphysema group, 2.5.

From this small pilot study it seemed that the IJ segment would be best suited for study of the respiratory variation of the ballistocardiogram. The IJ of all patients in all groups was then analyzed for the ratio of respiratory variation; that is, $\frac{\text{Amplitude of Inspiratory IJ}}{\text{Amplitude of Expiratory IJ}}$.

In comparing the respiratory variation of IJ in each of the clinical conditions under study, the average of two inspiratory and the average of two expiratory complexes were used for the calculation of ratio. The results of these calculations can be seen in Fig. 2. The mean of the $\frac{\text{inspiratory}}{\text{expiratory}}$ ratio for the normal group was 1.5; that for the hypertensive group, 1.9; for the coronary artery disease group, 2.2; and for the emphysema group, 2.7.

When the difference between mean respiratory ratios is expressed as standard error,[16] there is a 4.5 standard-error difference between the mean ratio of the normal group and the mean ratio of the hypertensive group. The mean of the normal group differs significantly from that of all other groups, since there would be more than 4.5 standard-error difference. The difference between the mean ratio of the coronary disease patients and the hypertensive group is not statistically significant, however, since they differ by only a 2.3 standard error. There is a 2.8 standard-error difference between the means of the coronary disease group and the emphysema series, and a 4.8 standard-error difference between the mean ratio of the emphysema and the hypertensive groups. In other words, there is a significant difference in mean respiratory ratio of the IJ between all groups with the exception of that between the hypertensive and the coronary disease groups.

If one rather arbitrarily chooses a ratio of 2.0 or above as abnormal, then 7.5 per cent of the normal group, 36 per cent of the hypertensive group, 51 per cent of the coronary disease group, and 84 per cent of the emphysema group have an abnormal ballistocardiogram on the basis of respiratory ratio of IJ alone. If one were to place this arbitrary limitation of normality at 1.8, then 19 per cent of the normal group, 54 per cent of the hypertensive group, 64 per cent of the coronary disease group, and 94 per cent of the emphysema group would be abnormal on the basis of respiratory variation. If this ratio were revised upward to define as abnormal a ratio of 2.2 or above, then 2.5 per cent of the normal group, 23 per cent of the hypertensive group, 36 per cent of the coronary disease group, and 71 per cent of the emphysema group would be abnormal on the basis of respiratory variation.

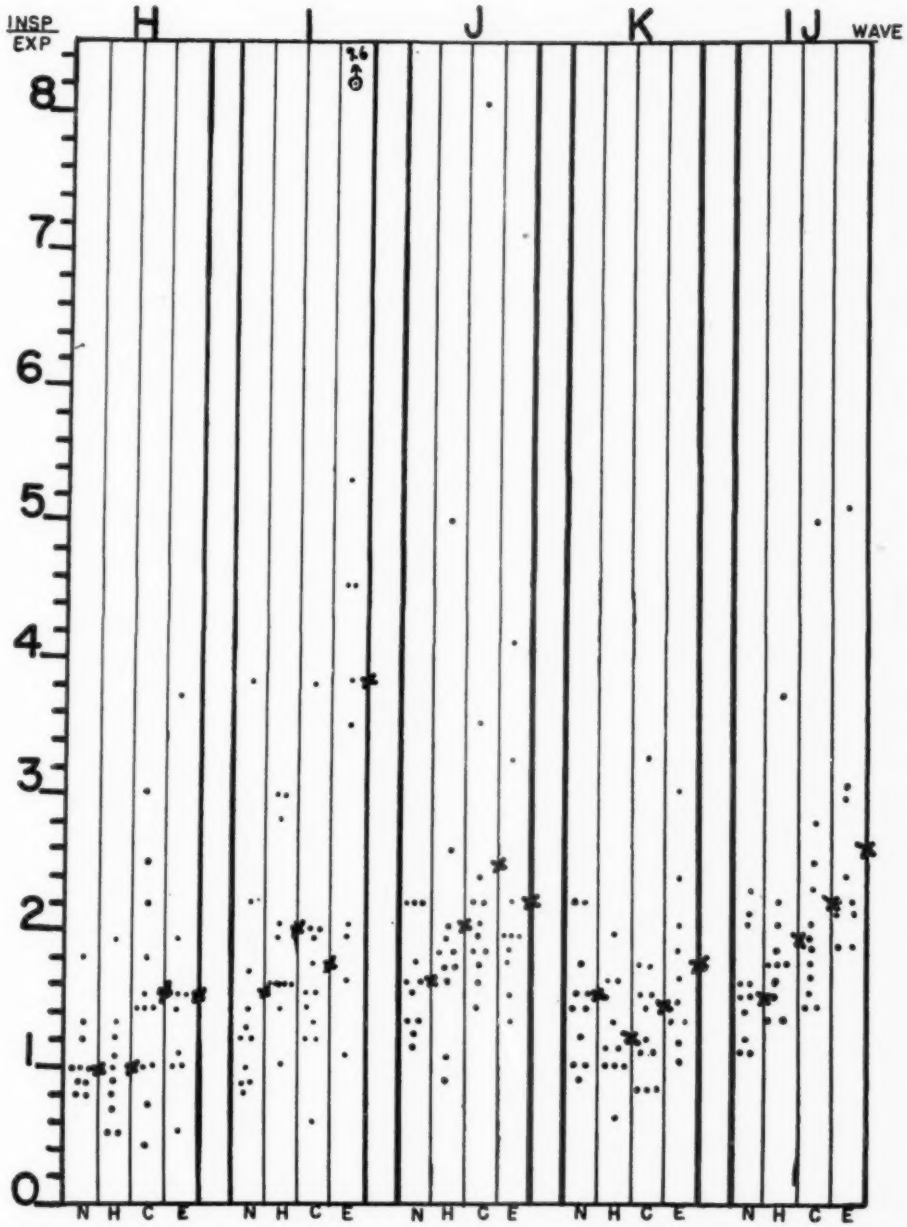

Fig. 1.—Respiratory Ratio of *H*, *I*, *J*, *K*, and *IJ*. *N*—Normal; *H*—Hypertensive; *C*—Coronary artery disease; *E*—Emphysema. Scale refers to the Inspiratory/Expiratory ratio of H, I, J, K, and IJ waves of the ballistocardiogram. *X* is the average ratio for each group.

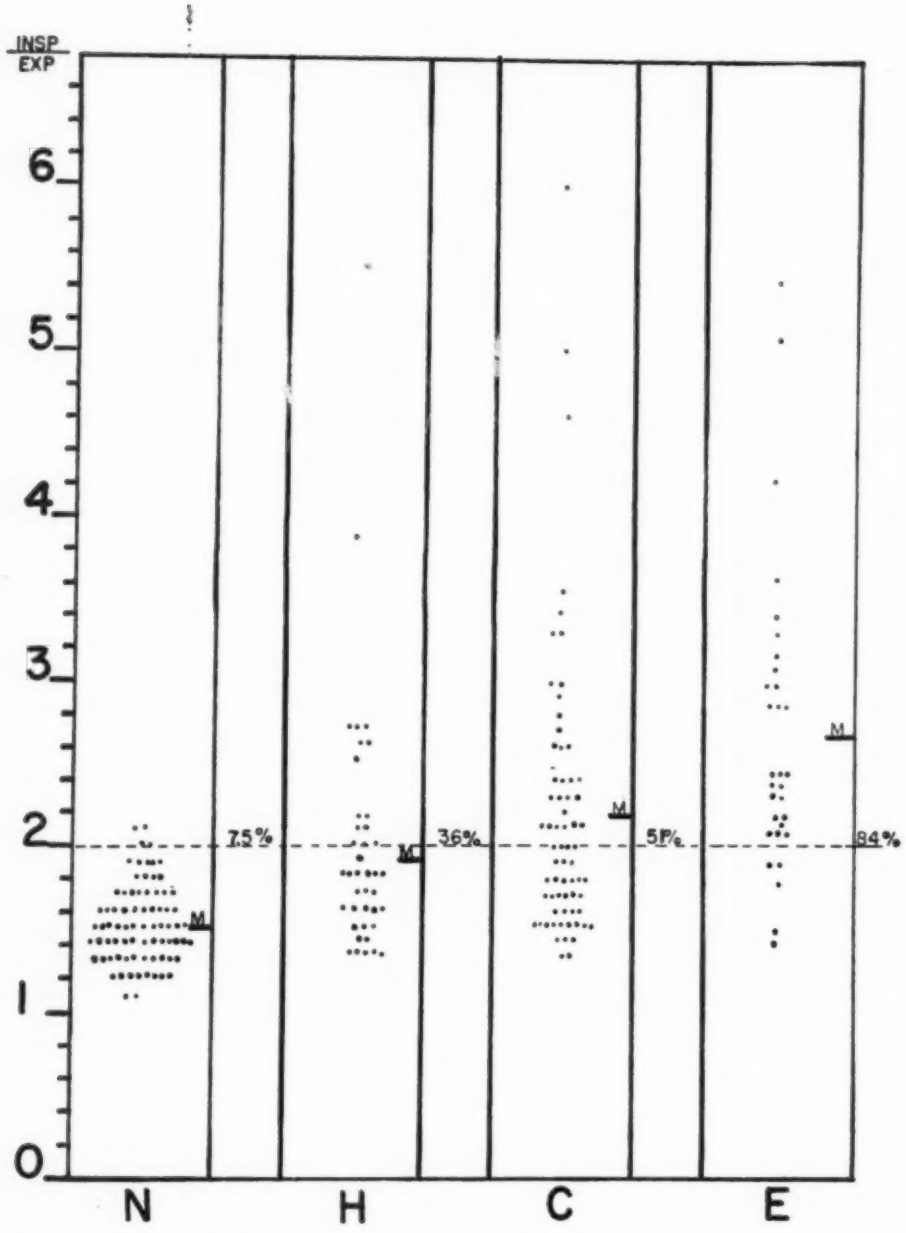

Fig. 2.—Respiratory Ratio of IJ. *N*—Normal; *H*—Hypertensive; *C*—Coronary artery disease; *E*—Emphysema. Scale refers to the Inspiratory/Expiratory ratio of the IJ. *M* designates the mean for each group. All values at or above the broken line are abnormal if one chooses a ratio of 2.0 or greater as abnormal; percents refer to the percent abnormal in each group on this basis.

Thus, it can be seen that given a patient with a respiratory ratio between 2.0 and 2.5 one would be unable on the basis of the ratio alone to decide between coronary disease, hypertension, or emphysema but could accurately pick "normal" from "abnormal". An aid to such differentiation can be gained from Fig. 3 wherein a typical ballistocardiogram from each of the four groups under study is presented. The normal ballistocardiogram presents a low respiratory ratio with a definite and regular pattern and a relatively constant HK time. The ballistocardiogram of the hypertensive patient presents some increase in respiratory ratio,

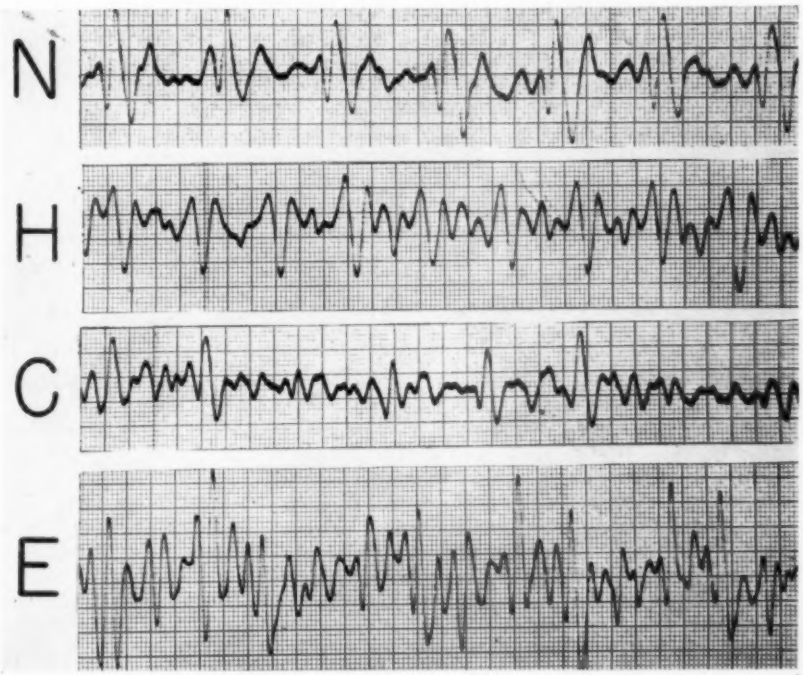

Fig. 3.—Representative ballistocardiograms. *N*—Normal; *H*—Hypertensive; *C*—Coronary artery disease; *E*—Emphysema.

a fairly regular and definite pattern with shallow I, deep K, and rather high L waves. The ballistocardiogram of the patient with coronary artery disease presents an increase in respiratory ratio, decreased amplitude in expiration, irregular though fairly definite, and some increased variation in HK time. The ballistocardiogram of the patient with emphysema presents an increase in respiratory ratio with the variation predominately in the I wave, while the pattern remains fairly regular and definite with little variation in HK time.

When all of the data pertaining to amplitude of IJ in each of the groups is analyzed and the inspiratory and expiratory values comprising the previous ratios are plotted separately, another clue to differentiating the cause of the increased respiratory ratio is seen. By considering first the absolute values of the inspiratory amplitudes in Fig. 4, the average of the normal group is 19.8 millimeters; that of the hypertensive group, 14.3 mm.; the coronary disease group, 10.5 mm.; and that of the emphysema group, 22.3 mm.

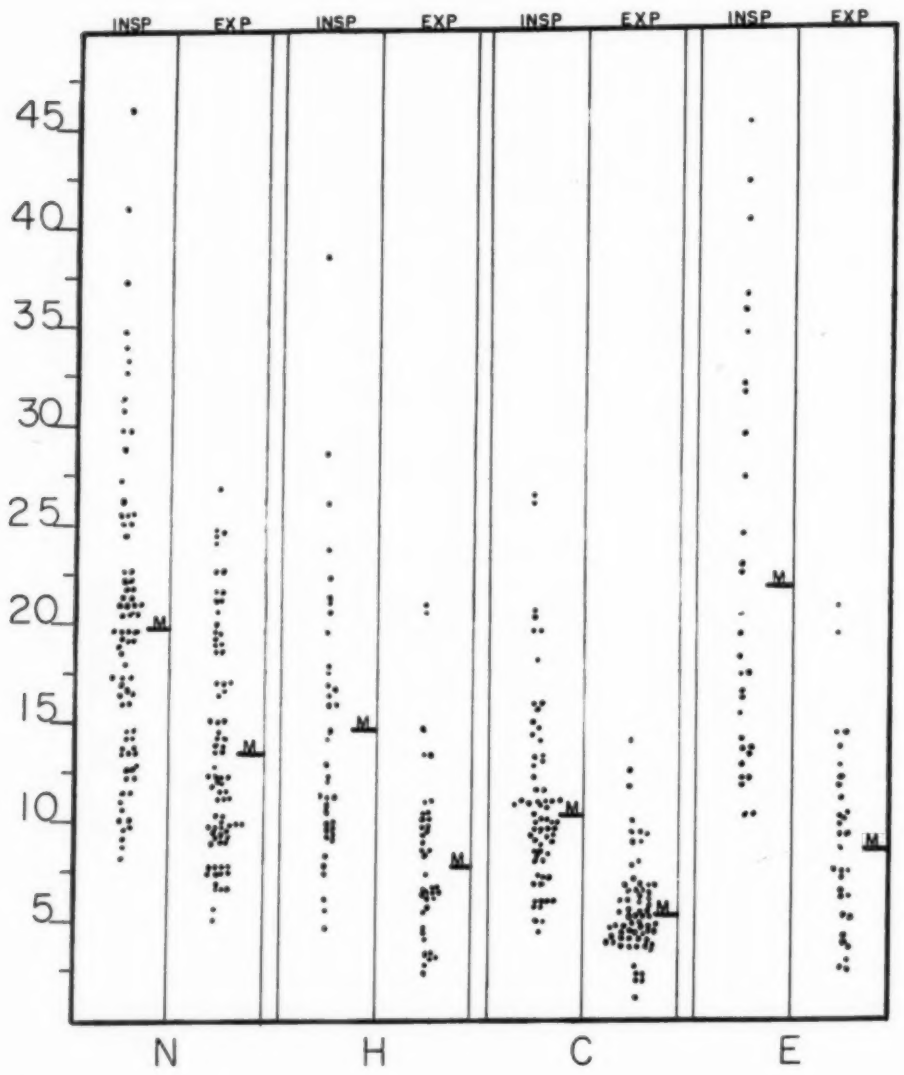

Fig. 4.—Absolute amplitude of IJ in inspiration and in expiration. N—Normal; H—Hypertensive; C—Coronary artery disease; E—emphysema. Scale is amplitude of IJ in millimeters. *M* indicates mean amplitude of each group. Insp.—Inspiration; Exp.—Expiration.

The difference between the average inspiratory IJ for the normal group and the emphysema group is less than 2.5 standard error and is not significant. However, the average inspiratory IJ of the coronary disease group differs from that of the hypertensive group by more than 2.5 standard error and also from those of the normal and emphysema group by more than 2.5 standard error. These differences are therefore significant. If one arbitrarily decides that an inspiratory amplitude of 10 mm. or less is abnormal, then 8.9 per cent of the normal group, 33 per cent of the hypertensive group, 54 per cent of the coronary disease group, and 0 per cent of the emphysema group are abnormal in this respect.

The average expiratory amplitude for the normal group is 13.2 mm.; for the hypertensive group, 7.9 mm.; for the coronary disease group, 5.4 mm.; and for the emphysema group, 9.0 mm. The difference between the mean of the normal group and the emphysema group is 13.5 standard error and is significant; the mean of the normal group differs from the mean of the other two groups by more than 13.5 standard error. The difference between the means of the hypertensive and emphysema group is not significant; the mean of the coronary disease group is significantly different from that of all other groups.

If, from Fig. 4, one chooses an expiratory value of 7 mm. or less as abnormal, then 7.6 per cent of the normal group, 51 per cent of the hypertensives, 85 per cent of the coronary group and 39 per cent of the emphysema group would have to be classed as abnormal.

The percentage of ballistocardiograms found to be abnormal in each group employing one or more of the criteria given here, as well as the grading system of Brown and associates,[1] is given in Table I.

TABLE I. PERCENTAGE OF ABNORMAL BALLISTOCARDIOGRAMS IN PATIENT GROUPS BY VARIOUS CRITERIA

BASIS OF ABNORMALITY	RESP. IJ RATIO 2.0 OR GREATER (%)	INSP. IJ 10 OR LESS (%)	EXP. IJ 7.0 OR LESS (%)	RATIO 2.0 OR GREATER, INSP. IJ 10 OR LESS, EXP. IJ 7 OR LESS (%)	BROWN GRADE 2 OR MORE (%)	RATIO 2.0 OR GREATER, INSP. IJ 10 OR LESS, EXP. IJ 7 OR LESS, GRADE 2 OR MORE (%)	RATIO 2.0 OR GREATER, GRADE 2 OR MORE (%)
Normal	7.5	8.9	7.5	13	2.5	13	7.5
Hypertensive	36.0	33.0	51.0	62	85.0	92	92.0
Cor. Artery Disease	51.0	54.0	85.0	87	85.0	93	91.0
Emphysema	84.0	0.0	39.0	84	77.0	97	97.0

It can be seen that if one determines abnormality for each group by a respiratory ratio of 2.0 or greater and a Brown grade of 2 of higher, we find that 7.5 per cent of the normal persons, 92 per cent of the hypertensive patients, 91 per cent of the coronary disease patients, and 97 per cent of the emphysema patients will fall into the abnormal group.

The results of the ballistocardiograms of the fifth heterogeneous group with one or more diseases are listed in Table II. As noted previously, this group is too small to permit definite conclusions.

TABLE II. RESULTS OF BALLISTOCARDIOGRAMS IN PATIENTS WITH COMBINATION OF DISEASES

AGE	DIAGNOSIS	GRADE BCG	INSP./EXP. AMPLITUDE MM.	RATIO
52	Hyp.-Cor. dis.	2	10.6/3.8	2.8
52	Hyp.-Cor. dis.	2	12.1/4.8	2.5
45	Hyp.-Cor. dis.	3	9.3/7.0	1.3
65	Hyp.-Cor. dis.	3	7.0/5.0	1.4
53	Hyp.-Cor. dis.	0	34.5/30.0	1.2
51	Hyp.-Cor. dis.	3	8.8/3.0	2.9
69	Hyp.-Cor. dis.	3	6.8/3.5	1.9
55	Hyp.-Cor. dis.	3	6.5/2.8	2.3
48	Emp.-Cor. dis.*	2	33.0/15.0	2.2
52	Emp.-Cor. dis.	3	7.0/4.0	1.7
56	Emp.-Cor. dis.	3	6.5/2.5	2.6
72	Emp.-Cor. dis. and Hyp.	2	14.0/7.5	1.9

*The only criterion for coronary disease in this patient was a right bundle branch block.
Hyp. = Hypertensive; Emp. = Emphysema; Cor. Dis. = Coronary artery disease.

DISCUSSION

The respiratory changes in diastolic filling of the right ventricle may be clinically ascertained by noting the inspiratory collapse of dilated chest wall veins which communicate with the chest cavity. This state is seen in patients with some intrathoracic venous obstruction.

This clinical observation, which must have been known for many years, was experimentally confirmed in dogs, where it was found that the combined diastolic volume and stroke output of the two ventricles were augmented with inspiration and diminished with expiration.[17] Shuler and associates[18] were able to show in dogs that during inspiration the diastolic size and stroke volume of the right ventricle were greater than in expiration, and that diastolic size and stroke volume of the left ventricle were greater in expiration than inspiration. These changes were synchronous with fluctuations of intrathoracic pressure accompanying normal respiration. Similar respiratory effects were demonstrated for man by Starr and Friedland,[19] who also studied the effect of changing heart position on normal respiratory variation of the ballistocardiogram. They concluded that the normal ballistic respiratory variation was not due to change in heart position but was the result of pressure changes in the chest causing blood to be "inspired" into the chest cavity with inspiration and expelled with expiration. Brown and associates[1,2] in reviewing the literature and from their own work with respiratory variation in pathological states arrived at a similar conclusion regarding the genesis of the normal ballistic respiratory variation of IJ.

The respiratory variation of IJ which is seen in the ballistocardiogram of the hypertensive patient is not due to the blood pressure elevation per se. Early in the course of the asymptomatic hypertensive patient, the ballistocardiogram is frequently normal. Increased respiratory variation may be due to the inability of the dilated and/or hypertrophied left ventricle to respond maximally to diastolic filling. Systolic ejection is often not as rapid as normal in the left ventricle of such a heart. The diastolic volume of blood in the left ventricle is increased, and output of the left ventricle does not change as much as is normally expected with phases of respiration; therefore, the ballistocardiogram actually reflects the respiratory changes of the right ventricular output. Since we are using an instrument which is greatly influenced by velocity, we would therefore expect smaller amplitudes when the left ventricle predominates in the production of the ballistic pattern, as it does in expiration.

Several causes have been suggested for the increased respiratory variation which is frequently seen in coronary artery disease. Brown and associates[1-3] have suggested a peripheral and splanchnic pooling of blood in some instances, thus reducing right ventricular output to a rather critical level so that left ventricular output in turn is so low that coronary artery filling is inadequate. This concept is supported by clinical, electrocardiographic, and ballistocardiographic improvement which some anginal patients derive from the use of an abdominal binder. Brown has also suggested a critical diminution of the pulmonary blood pool as another cause of the respiratory variation with coronary artery disease. This would permit only inadequate filling of the left ventricular cavity. It appears, however, that the cause of the increased respiratory variation in the majority of instances of coronary artery disease is damage to the left ventricular myocardium.[20] This rather specific damage to the left ventricular musculature permits the right ventricular respiratory variation to predominate ballistocardiographically,[3] and as in the case of hypertensive cardiovascular disease, the left ventricular output varies less during the respiratory cycle than is normally seen.

The increased respiratory variation of the emphysema patient would seem to be due to one or more of three possible mechanisms. At least a certain amount of the respiratory variation is merely an exaggeration of the condition that obtains in the normal individual. This exaggeration is due to the greater variation in intrapleural pressure which is seen with emphysema, as well as to some consequent reduction in the pulmonary blood pool.[3] In some instances, however, we find the typical respiratory variation without evidence of impedance to expiration. This variation is apparently due to a decreased pulmonary blood pool as seen in the three pneumonectomized patients of our group. The third contributory cause is positional; in inspiration the heart becomes quite vertical and the cardiac ejection vector is more nearly parallel to the longitudinal axis of the body. In expiration the vector of ejection becomes more horizontal. Experimental evidence for this latter concept can be gained by noting the rather marked respiratory variation of the I wave in the emphysema group as compared to the other groups of patients. The variation of the IJ in emphysema, therefore, is due to changes

in pressure relationship, pulmonary blood pool, and position rather than to any involvement of the ventricular musculature. The difference to be seen between the tracings of coronary artery disease patients and emphysema patients certainly supports this concept. Both groups have an abnormal ratio of $\frac{\text{Inspiratory IJ}}{\text{Expiratory IJ}}$, and these ratios are only slightly different in the two groups. However, the emphysema group has a normal inspiratory amplitude of IJ. Both groups have an average expiratory IJ amplitude significantly different from that of the normal group; the coronary disease average is even lower than that of the emphysema patients.

The results of the study on the twelve patients with various combinations of the three disease states suggest that when coronary artery disease is present with another condition, the record is more likely to reflect the weakened, malfunctioning left ventricular musculature associated with coronary artery disease rather than the dysfunction associated with emphysema or hypertension. This is to be expected from the foregoing discussion regarding the genesis of respiratory variation in the various conditions.

The diagnostic accuracy of the electromagnetic ballistocardiogram in our patients compares very favorably with that reported by others who used the electromagnetic,[8,23] photoelectric,[21,22] or Starr bed[1,3] ballistocardiographs. From the results of this study it would appear that the Brown[3] system of grading and the determination of respiratory ratio of IJ provide the best and most practicable diagnostic criteria for ballistic abnormality. The measurement of absolute amplitudes and the definition of normal in terms of such amplitudes should be avoided, since other electromagnetic ballistocardiograms will be slightly different in construction from the one employed in this study and the instrument cannot be standardized to make absolute amplitudes comparable among different patients. Regardless of construction, the respiratory ratios and gradings should be comparable. In addition to this most practical consideration, it can be ascertained from Table I that to define an abnormal ballistocardiogram as one with a respiratory ratio of IJ of 2.0 or greater, and a grade of 2 or greater, yields the maximum number of abnormal tracings in the three diseased groups with the minimum number of "false positives". (An unknown number of these "false positives" may have early or latent disease.) Although the employment of grading alone gave only 2.5 per cent "false positives", it was felt that this criterion also permitted too many false negatives in the emphysema group when compared with the combination of grading and respiratory ratio. However, the addition of respiratory ratio to grading did not significantly increase the number of abnormal records in the coronary disease group.

There may be some question as to whether the ballistocardiographic differences between the various groups may not be partially due to difference in age. As noted, the normal group averaged 35 years in age, the hypertensive group 50 years, the coronary disease group 56 years, the emphysema group 52 years. The average age of the normal group differs significantly from that of all other groups, there being a difference of 10 standard error between the mean age of this group and the hypertensive group. There is also a significant difference in mean age

between the coronary disease group and the hypertensive group (3.4, S. E.) but no significant difference between that of the coronary group and the emphysema group. Starr and Hildreth[29] recently observed that the average amplitude of the I and J waves decreased slowly with advancing age and that this decrease was greater for the expiratory portion of the ballistic tracing. This decrease was so slow, however, that a period of more than 10 to 14 years was necessary in order to detect it. A further abnormality detected with aging was the decrease in depth of the I wave and its actual rise above the base line as the age increased beyond 55 to 60 years. From this it appears that ballistocardiographically there may not be a significant difference in age between any of our groups of diseased patients and that the age difference between our normal group and the diseased groups (average 15 to 21 years) is just borderline for significant ballistocardiographic difference on the basis of age alone. It was impossible to determine from Starr's data whether or not the normal respiratory ratio will be increased to 2.0 or above during 15 to 20 years increase in age between 30 to 50 years. Although the normal group was not comparable in age to the diseased patients, this need not impair the validity of the observations.

Since Starr states that the difference occurring in this age group is not sufficient to be statistically significant, it appears that the respiratory ratio should not be seriously influenced by aging alone in this age range.

It should be emphasized that the results of this study apply only to the electromagnetic ballistocardiogram. It is possible that there may be some application to the photoelectric and high-frequency bed type of recording system. It has been shown in a recent study[24] that a normal ballistocardiogram may be obtained with a displacement recording device in the presence of known coronary disease and in which an abnormal tracing was recorded with a velocity-measuring ballistocardiograph. One would, therefore, expect the results of this study to be more applicable to the high-frequency bed than to the photoelectric instrument.

CONCLUSION

In this study of the respiratory variation of the electromagnetic ballistocardiogram, the H and K waves appear to be of little or no value in detecting abnormalities in respiratory variation. The I wave varies with the phase of respiration, being most variable in patients with emphysema. The J wave varies with respiration and is most variable in patients with coronary artery disease. The amplitude of the IJ stroke appeared to be best suited for indicating ballistic respiratory variation. The mean respiratory ratio of IJ of the normal individuals was significantly different from all other groups. There was also a significant difference between the mean respiratory ratio of the emphysema patients and all other groups; however, the hypertensive and coronary disease groups did not differ from each other. The inspiratory IJ of the normal and emphysema groups did not differ significantly, although both differed significantly from the hypertensive and coronary disease patients. The amplitude of IJ in expiration for the normal subjects was significantly different from all other groups. That of the coronary group was also significantly different from all others in expiration, while the emphysema and hypertensive groups did not differ significantly.

SUMMARY

1. A short review of the variation in cardiac output with phases of the respiratory cycle is given.

2. The normal respiratory variation is defined as

$$\frac{\text{Amplitude of Inspiratory IJ}}{\text{Amplitude of Expiratory IJ}}$$

which is less than 2.0. An increased ratio is found in coronary artery disease, hypertension, and emphysema.

3. A method of differentiating the coronary disease patient from the emphysema patient ballistocardiographically is suggested.

4. When a patient presents a combination of coronary artery and other disease, his ballistocardiogram is usually of the type seen in coronary disease.

5. The genesis of ballistic respiratory variations of the normal, the hypertensive, coronary disease, and emphysematous patients is discussed.

6. Of the criteria examined for interpretation of the electromagnetic ballistocardiogram, a combination of the Brown grading system and respiratory ratio of 2.0 or greater served best to differentiate between normal individuals and those with cardiac or chronic pulmonary disease.

The authors are indebted to Dr. William Dock for aid in the construction of the ballistocardiograph, and to our consultant in Cardiovascular Disease, Dr. Nahum Winer of the Lenox Hill Hospital, New York City, for many helpful suggestions and a critical review of the manuscript.

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THE EFFECTS OF CIGARETTE SMOKING ON THE BALLISTOCARDIOGRAMS OF HIGH SCHOOL YOUTHS

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THE observation originally made in this clinic[1] that smoking a cigarette may alter the ballistocardiograms of healthy young men (28 to 35 years) from a normal to an abnormal trace has been amply confirmed.[2] While personal idiosyncracy seemed a possible explanation we have further observed that this alteration is extremely common in patients with known coronary artery disease and rare before the age of 30. Because of these observations, it has been suggested that an abnormal ballistocardiogram following smoking usually is due to coronary disease and not to "tobacco sensitivity" with no organic defect. It was decided to test this hypothesis by studying the ballistocardiogram during cigarette smoking in a group of high school lads, under 18 years of age but habitual smokers, and unaware of any sensitivity to tobacco as are the older subjects formerly reported. The incidence of significant coronary disease in such a group would be very low.

METHODS

A group of 100 high school boys between the ages of 14 and 18 years were the subjects of this study. These lads were all in good health, and all were habitual smokers for the past 2 to 5 years. The ballistocardiograms were obtained by the Dock type of electromagnetic ballistocardiograph and recorded on a conventional one-channel direct-writer electrocardiograph. The electrodes of Lead II were placed in series with the ballistocardiograph so as to impose the QRS complex on the ballistocardiogram as a timing device.

The tests were conducted from 2 to 4 hours after breakfast. Most of the students had abstained from tobacco on the morning of the studies. None of them had smoked in the hour preceding the tests. After a control trace was obtained, a standard brand of cigarette was smoked. A second record was made just after the final puff of the cigarette. The ballistocardiograms were obtained during normal respiration since increased respiratory variation of the systolic complexes was the most frequent abnormality seen in other subjects.

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RESULTS

Upon perusal of our data, ten records were discovered to be either distorted with artifacts or abnormal. The ten authors of these ballistocardiograms were recalled and the experiment was repeated. All control traces were normal upon re-examination.

Thus, no example of an abnormal ballistocardiogram was seen in the control series, although it is unlikely that all these lads were free of rheumatic heart disease.

The most frequent response to smoking was an increase in heart rate. Ninety-four of the hundred subjects responded with an accelerated pulse. The average pulse rate in the control studies was 70 per minute, rising to 83.5 per minute after completion of a cigarette. The greatest increase was from 55 per minute to 93 per minute.

In spite of the increase in rate, the I-J wave only rarely decreased in amplitude with smoking but usually remained about the same. We did calculate the cardiac output from the ballistocardiogram, but the inference would be that stroke volume was constant with minute volume increased.

Two of the subjects responded to smoking with an abnormal degree of respiratory variation of the amplitude of the I-J waves and three others to a lesser degree. We consider respiratory variation significant when the largest I-J wave is more than twice as large as the smallest I-J wave in one respiratory cycle (Brown, Grade 1).

We observed the L wave to become enlarged in five cases after smoking, but the heart rates in these examples were about 100 per minute when large L waves usually appear. Therefore, we believe that these are a function of rate rather than a direct effect of smoking. Aside from the increased L waves, no large diastolic waves were observed. In no cases were diastolic waves larger than the I-JK complex even during expiration. This contrasts sharply with the findings in the men 28 to 35 years old who showed striking response to smoking.[1]

DISCUSSION

Our data confirm other reports[1,3] that an increase in the pulse rate is the most frequent response to smoking. However, our data differ from others[1,2] in the infrequency of abnormal responses to smoking. Most of the subjects of other investigators were over 20 years of age, but Scarborough found no marked abnormality in any subject under 30.[4]

In Fig. 1 is illustrated the most marked degree of abnormality found in this series. It can be observed that in the control trace there is a borderline respiratory variation of the I-J waves with the largest of these complexes measuring 19 mm. in height, whereas the smallest is 10 mm. The pulse rate rose from 80 to 100 with smoking. After smoking the average I-J wave decreased in amplitude from 14 mm. to 10 mm. If the minute volume is estimated from these data, no change is noted. It can also be observed that L waves, which were prominent in the control, further enlarged with smoking. We interpret such changes as minor.

The observations recorded here do not support the thesis that individual sensitivity to nicotine is the cause of the abnormal response to smoking in apparently healthy people. Caccese assumed that the abnormal trace seen occasionally after smoking represented a poor habituation to tobacco.[1] If this were so, then a significant incidence of abnormality would be expected in young smokers. In 100 consecutive youths no major abnormalities were seen and only two examples of a minor degree of abnormality were found.

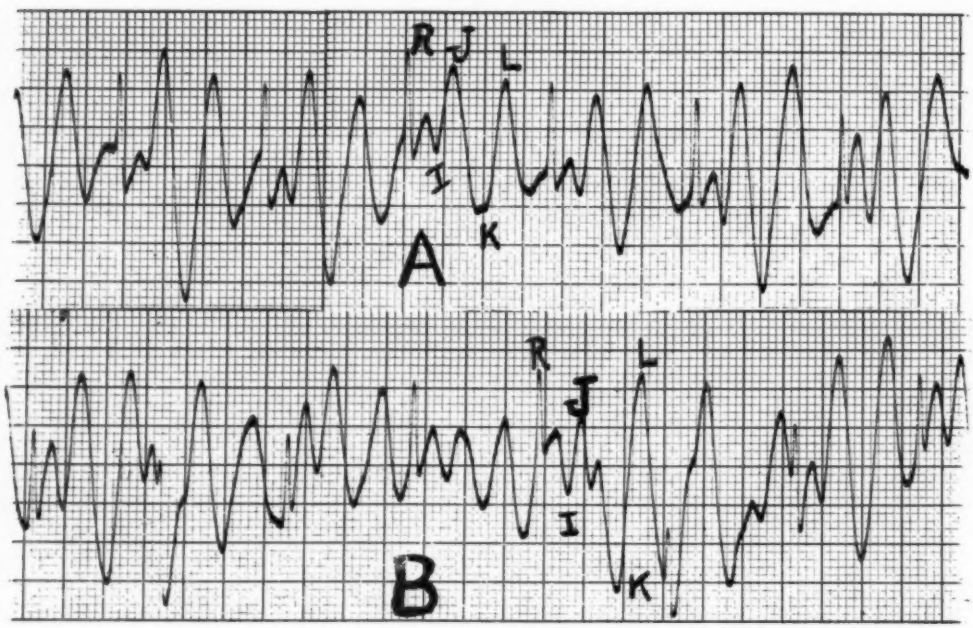

Fig. 1.—*A*. Control ballistocardiogram; *B*. Trace on same subject immediately after smoking one cigarette. *R* refers to *R* waves of the electrocardiogram which has been superimposed on the ballistocardiogram as a timing device. Further comment in the text.

The conclusion that there is a relationship between abnormal response to smoking and atherosclerosis is strongly supported by the recent investigations of Davis and associates[5] who demonstrated an extremely close correlation between deterioration of the ballistocardiogram after tobacco and the presence of known coronary artery disease. These investigators actually demonstrated a much higher correlation of coronary artery disease with the smoking test than with either the anoxemia or the double Master's two-step test.

In spite of the high correlation of changes of the ballistocardiogram to smoking and coronary artery disease, the smoking test does not reflect a positive response to a moderate degree of coronary arteriosclerosis since abnormal traces following tobacco are rare before 30; yet Lober,[6] in an exhaustive investigation, demonstrated the process of coronary sclerosis beginning in infancy and progressing through life. Lober's data on the degree of atherosclerosis show an increase in the rate of change of sclerosis in the third decade of life just when

abnormal ballistocardiographic responses to smoking appear. Autopsies on American soldiers dying as battle casualties in Korea revealed 77.3 per cent of this group with an average age of 22.1 years to have gross evidence of coronary artery disease but only about 10 per cent exhibited advanced disease with over 70 per cent occlusion of the lumen of one major vessel.[7]

SUMMARY

1. No abnormal resting ballistocardiograms were found in a consecutive series of 100 healthy high school lads.

2. Smoking a standard brand cigarette produced no real abnormalities of the ballistocardiogram in this age group whereas this is a common phenomenon in older subjects.

3. A significant increase in respiratory variation of the I-J waves (Grade 1) occurred in only two subjects; lesser increase in this variation was noted in three others.

4. The most frequent response to smoking was an increase in pulse rate, with minimal evidence of change in stroke volume, judging from the amplitude of the systolic waves.

5. The significance of these observations is discussed.

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BALLISTOSCOPE RECORDING WITH THE AID OF AN ASYMMETRICAL SHUTTER

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IN A previous report[1] the ballistoscope has been described as an instrument which allows the bedside observation of the transmitted cardiac impulse in the form of a two-dimensional vector loop. The ballistoscope as employed in the present study is essentially a small aluminum container, half-filled with commercial heavy oil which serves as a reflecting surface. When the instrument is placed upon the anterior chest wall with the subject in a supine position the light of an otoscope bulb kept at a distance above the ballistoscope produces a reflected image within the container which is synchronous with and characteristic of the particular cardiac impulse. In the normal individual it appears as an elliptic loop with a counterclockwise rotation direction and a long axis which is usually in a longitudinal or near longitudinal position (Fig. 3, A). The size of the loop depends upon the magnitude of the cardiac impulse. It also increases proportionately with the distance between light bulb and oil surface within the container.

Previously, the otoscope bulb had been fixed to the instrument by means of a metal rod for the purpose of maintaining a constant distance between light source and reflecting surface. At present, however, the bulb has been detached from the ballistoscope in order to allow the hermetic closure of the instrument with an aluminum cover and to facilitate its use as a portable instrument. For bedside and office examination an ordinary battery otoscope serves as a light source.

For photographic recording purposes the otoscope bulb *c* is attached to the horizontal arm *b* of a rectangular stand (Fig. 2) which is adjusted so that the distance between light source and oil surface within the container is 20 centimeters. In this case the current is provided by a transformer supplying 2.5 volts.

Although the photographic procedure utilized in the original report attempted to differentiate the beginning from the end of the tracing by a gradually increasing intensity of the light at the onset of the exposure as compared with its abrupt ending by the shutter at the end of the exposure, it seemed that a method with a more frequent or perhaps continuous mode of identifying the rotation direction during the entire duration of the exposure would present a distinct advantage in contrast to the single mode of identifying the rotation direction

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as described previously. This problem attained greater significance when it was found that the ballistoscopic loop as observed over the precordium of the normal individual has a counterclockwise rotation direction, while a clockwise rotation direction is commonly associated with heart disease. This problem seems to have been solved by the method of the continuous asymmetrical shutter as employed in this study. This method is based upon the interruption of the light emanating from the otoscope bulb *c* (Fig. 2) by a rotating disc *a* with perforated segments which permit the passage of light for periods of 0.005, 0.01, and 0.02 second, consecutively, each of them separated by a dark period lasting 0.005 second. The time ratio of the three segments is 1:2:4. Because this sequence is the simplest asymmetrical order and cannot possibly be confused with the reverse sequence of 4:2:1, it permits the instantaneous recognition of the rotation direction of the ballistoscopic loop in the photographic recording during all phases of the exposure which lasts 0.5 second.

DESCRIPTION OF BALLISTOSCOPE

As seen from Fig. 1 the ballistoscope is an aluminum cylinder, 5 cm. high, the base of which has a diameter of 6.25 centimeters. Its upper portion has a cylindrical excavation, 3.25 cm. in diameter and 2.5 cm. in depth, serving as a container which is half-filled with a dark, viscous fluid, such as commercial heavy oil, number 40. The rim of this container provides a groove fitting for a tight-closing aluminum cover. The bottom of the ballistoscope has in its center an opposite, smaller excavation, 2.5 cm. in diameter and 0.75 cm. in depth which by means of a short hollow metal rod piercing the aluminum shell can be connected with a stethoscope in order to allow auscultation of the heart sounds. This in turn aids in the proper correlation of the ballistoscopic and auscultatory phenomena.

DESCRIPTION OF ASYMMETRICAL SHUTTER

The asymmetrical shutter (Fig. 2) is a disk *a*, 8 cm. in diameter mounted on the horizontal arm *b* of a stand with a heavy iron base. The horizontal arm which is 60 cm. long and holds an otoscope bulb *c* at its end can be moved vertically along the stand. A transformer supplies the otoscope bulb with a current of 2.5 volt. The horizontal arm also holds a small electric motor *d* which drives the disk by means of a gear transmission *e* at the speed of 1,200 revolutions per minute. The disk is made of thin aluminum and contains three open segments of 36°, 72° and 144°, respectively, separated by three solid segments of 36° each. During rotation of the disk the open segments permit the passage of light from the otoscope bulb for periods of 0.005, 0.01, and 0.02 second, consecutively, interrupted by dark periods of 0.005 second and corresponding to the three solid segments of the disk.

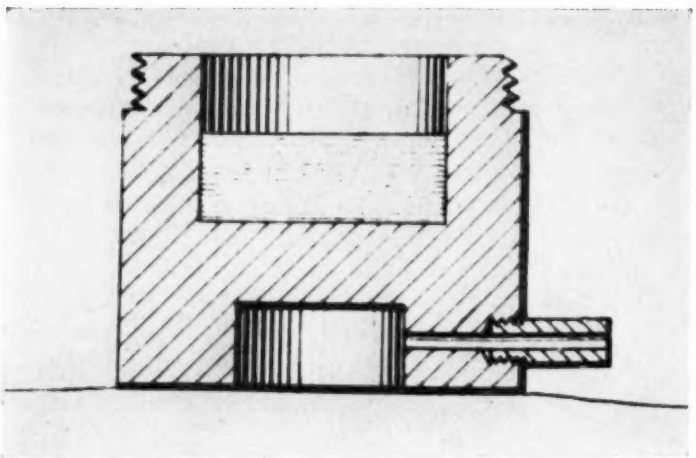

Fig. 1.—Ballistoscope cross section.

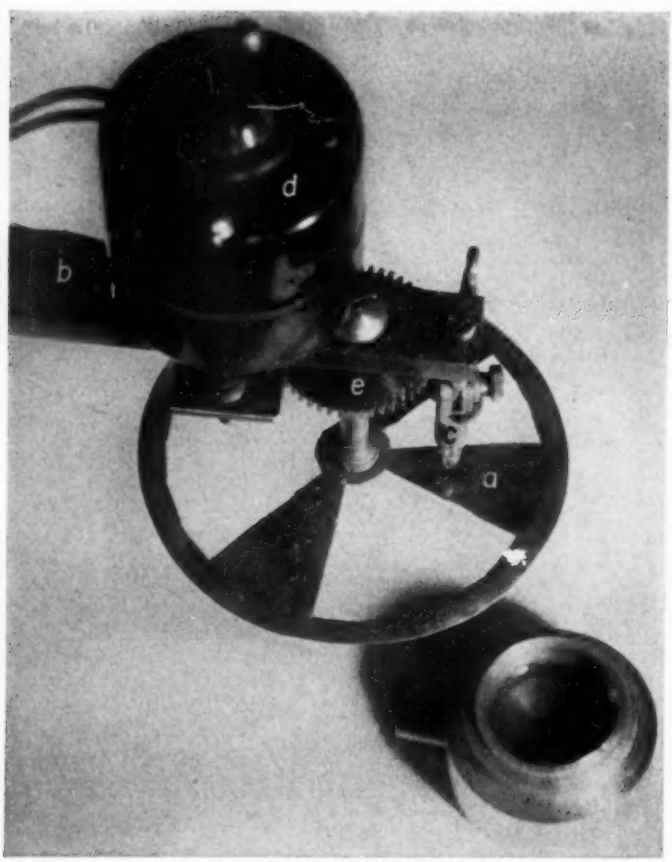

Fig. 2.—Asymmetrical shutter and ballistoscope in working position.

PROCEDURE

In order to observe the transmitted cardiac impulse the ballistoscope can be placed upon any part of the human body such as the anterior chest wall with the patient in a supine position, or upon the back with the patient in a prone position. It can also be placed upon a bar across the lower legs according to the procedure of Dock.[2] For purposes of obtaining a photographic record the horizontal arm *b* (Fig. 2) is placed at a distance of 20 cm. above the fluid surface within the ballistoscope so that the otoscope bulb is almost vertically above it. A camera is then placed in a symmetrical position to the bulb and focused upon the vector loop within the ballistoscope. While both the otoscope bulb and the shutter are turned on, the film is exposed for 0.5 second after synchronizing the exposure with the patient's pulse.

DISCUSSION

The problem of recognizing and recording the rotation direction of the ballistoscopic loop greatly resembles that encountered in vectorcardiography. Although the two methods are basically different, one representing the mechanical and the other the electrical forces associated with the cardiac impulse, the task of registering the rotation direction of the vector loop as caused by either one of them seems to have an apparent similarity. In vectorcardiography a high-speed moving picture camera can record the oscilloscope screen image.[3,4] The same principle has been successfully applied to the analysis of the ballistoscopic loop. It is realized, however, that the production of a moving picture for this purpose is not an ideal solution. On the other hand, the fragmentation of the vectorcardiographic tracing into portions, the beginning of which can be distinguished from the end by a change in width of each fragment, has succeeded in recognizing the rotation direction of the QRS loop.[5] Similarly, the ballistoscopic loop can be broken up into phases consisting of three fragments each and arranged in an asymmetrical fashion as presented in this study.

In forty normal adults of various ages the ballistoscopic loop was characterized by a counterclockwise rotation direction when examination was carried out with the ballistoscope placed over the lower third of the sternum or over the left side of the precordium (Fig. 3, A). It is particularly in this area where a clockwise rotation direction was found to be associated with organic heart disease.

Preliminary studies in twelve patients with acute myocardial infarction have revealed that a clockwise rotation direction of the ballistoscopic loop may be encountered in the early phase of this condition, though only in a transient fashion and returning to a normal counterclockwise rotation direction in most instances within a few days. In these cases the loop was also characterized by a wide lateral sweep.

Hypertensive heart disease with left ventricular enlargement is frequently associated with a clockwise rotation direction of the ballistoscopic loop. The early reversal of the rotation direction in acute myocardial infarction may be of diagnostic value, therefore, only in normotensive individuals.

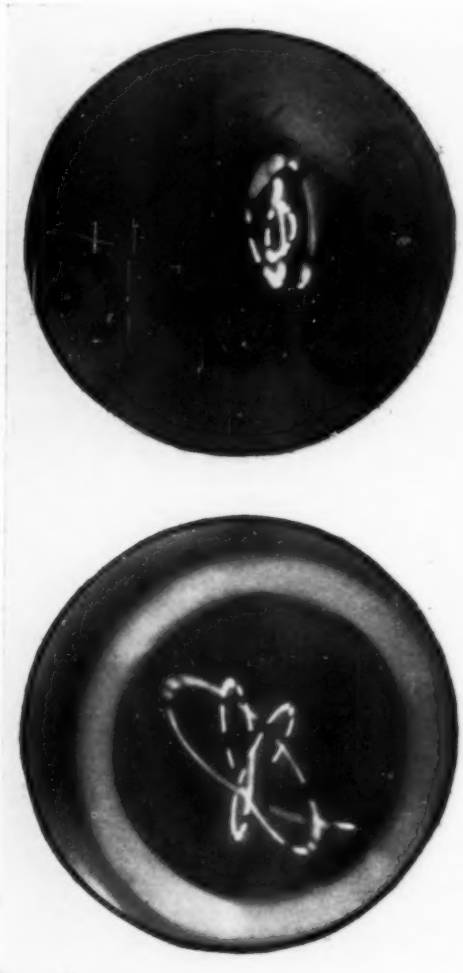

Fig. 3.—Ballistoscopic tracings: A, Normal individual; B, Patient with aortic insufficiency.

Some forms of rheumatic valvular heart disease may be associated with a clockwise rotation direction of the ballistoscopic loop. In six cases of aortic insufficiency with left ventricular enlargement the pattern was quite characteristic. Beside the very large excursion the rotation direction was clockwise (Fig. 3 B).

While eight patients with mitral stenosis without a considerable degree of mitral insufficiency displayed a counterclockwise rotation direction of the ballistoscopic loop, three patients with a pronounced degree of mitral insufficiency showed a clockwise rotation direction.

In two patients with thyrotoxic heart disease a clockwise rotation direction of the ballistoscopic loop was encountered which under goitrogenic therapy returned to a normal counterclockwise pattern within four weeks.

In a group of twenty patients with arteriosclerotic heart disease the rotation direction was both clockwise or counterclockwise. The pattern was found to be rather irregular but very well characterized by an exceedingly small excursion.

Although the ballistoscopic loop in these various conditions displayed rather striking patterns no given type of alteration can be described at this time as being produced by a given type of heart disease. Nevertheless, the clockwise rotation direction is a distinctly abnormal feature which may be of diagnostic help without being pathognomonic in any specific condition.

SUMMARY

1. The ballistoscope is an instrument which registers any motion of the underlying surface in the form of a two-dimensional vector loop.

2. The pattern of the ballistoscopic loop is constant and characteristic in normal individuals as well as in patients with various types of heart disease.

3. Photographic recordings of the ballistoscopic loop obtained with the aid of an asymmetrical shutter permit the immediate recognition of the rotation direction.

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VALUE OF ADDITIONAL THORACIC AND ABDOMINAL UNIPOLAR LEADS FOR DIAGNOSIS OF THE LOCATION AND EXTENSION OF MYOCARDIAL INFARCTIONS*

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SPA, BELGIUM

INTRODUCTION

THE use of the twelve routine leads, namely, the three standard leads, the three unipolar limb leads, and the six usual precordial leads for the electrocardiographic detection of cardiac infarcts and for the diagnosis of their location and extension, although usually satisfactory in practice, cannot be limitative.[20] These leads do not determine, for instance, the extension of lateral infarcts and do not always furnish unequivocal evidence of posterior or inferior infarcts, in spite of the use of the Leads V_F or aV_F, especially when the infarcts of this location are somewhat old. Several attempts have been made to remedy these difficulties. It has been proposed to explore the posterior wall of the heart by means of near unipolar leads from the lower end of the esophagus or from the stomach (Nyboer,[16] Burchell,[2] Deglaude and Laubry,[4] Brandes,[1]) but their use remains, as confess the protagonists of these methods, a complicated one in practice, nor do they prove very adequate in the acute or subacute stages of infarction. It has been suggested, on the other hand, to explore the lesions of the posterior wall by means of additional thoracic unipolar leads, including various dorsal leads, the more frequently used being V_7, V_8, and V_9, and to explore more especially the diaphragmatic aspect of the heart by the Lead V_E. As a general rule, these leads have been used only occasionally. However, the work of Grewin[8] on the usefulness of dorsal leads in the diagnosis of posterior infarction, the systematic survey of the diagnostic value of the Lead V_8 for the posterior infarction from Meyer and Schmidt,[12] the recordings of Leads V_7, V_8 and V_9 in several infarcts of various locations, made by Herrmann and associates[9] for a comparative study of the precordial leads in V, CR, CL and CF, must be pointed out. It has been admitted[6,19] that V_E is the choice lead† for the detection of the posteroinferior infarction (posteroseptal) as indicated by Wilson.[20] By generalization, however, one may see the Lead V_E considered as belonging to the semeiology of the plain posterior infarction that is mainly inferior or diaphragmatic (Soulié and Laham,[19] Routier,[17] Levy and Hyman[11]). However Soulié and Laham find

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†Editor's note: In North America, V_E is used to indicate the esophageal lead, while the British might use V_O for oesophageal leads. It would seem advisable to use V_X (xiphoid) instead of ensiform for the epigastric lead, and V_U for the umbilical lead instead of V_O (omphalos), and V_{XU} (between the two).

direct patterns of infarction in V_E (V_{E2}) in the cases of anterior infarction and of anteroinferior infarction and consider these as signs of septal involvement. Cabrera,[3] and Deglaude and Laubry[4] agree with that interpretation.

In the present study, a more systematic use of additional unipolar thoracic leads in the electrocardiographic examination of cardiac infarcts has furnished evidence that the data concerning them deserved to be more precisely stated and occasionally revised. Furthermore, the new data about the Lead V_E have led to interest in the registration of abdominal leads at a high level.

METHOD

In eighty-eight cases of myocardial infarction, clinically identified, (seventy-four men and fourteen women) of which the electrocardiographic features were pathognomonic in the standard limb leads, the augmented unipolar extremity leads and the six Wilson unipolar precordial leads, the evolution of two-thirds of which was followed, and additional unipolar leads were studied. For this, 217 complete electrocardiographic examinations were made. These concern only cases of which the tracings obtained in the twelve routine leads have shown characteristic Q and QS waves and, according to the age of the infarct, the monophasic wave or Pardee coronary wave or inverted symmetrical shaped T-deflection pattern in several leads. These tracings have been obtained from infarcts of generally different ages, the majority of them being examined, however, for the first time early after their onset (from 1 to 15 days, thirty-nine cases; fifty-three cases in the course of the first month; seventy-nine cases in the course of the first 4 months) and being followed repeatedly during their evolution. When the additional leads were recorded in cases of old infarctions, these were previously diagnosed with certainty by means of the clinical data and of repeated electrocardiographic examinations.

The cases of infarction studied may be divided, according to their location, as follows:

1. Infarctions of the anterior group, thirty-nine including: anterior, usually extensive, 20; anteroseptal, 7; anterolateral, 12.
2. Infarctions of the posterior group, forty-three, including: plain posterior, 33; posterolateral, 7; posteroseptal, 3.
3. Infarcts both anterior and posterior, 4.
4. Subendocardial infarcts, 2.

The additional thoracic and abdominal unipolar leads studied may be divided into three groups (Fig. 1):

1. Lead V_E from the tip of the ensiform cartilage.
2. Two leads on the median abdominal line, one at the level of the umbilicus (V_O), the other at the center of a line joining V_E and V_O, which may be called V_{EO}.
3. The lateroposterior Leads V_7, V_8 and V_9, the points of which have been located as usual on a horizontal line drawn at the level of V_4, on the left side of the chest, V_7, on the posterior axillary line, V_8, on the scapula angle line, V_9, at the left margin of the posterior spine.

All these additional leads were taken in the supine position.

The additional leads in normal subjects have been recorded in thirty-three normal subjects (22 men and 11 women) and provide the following information:

In V_7 and V_8, the QRS deflection often shows the left ventricular pattern qR, but an R or Rs pattern can also be met; the qR wave may first appear in V_8; Q waves of abnormal amplitude or duration or QS waves have never been met; the T wave is usually upward, being flat only twice in V_7 and three times in V_8.

In V_9, on the contrary, there is once a QS wave, five times a Q wave, the amplitude of which exceeds 25 per cent of that of the associated R wave, but the duration of which is only three times over 0.03 second; the S-T segment is depressed in five cases, the T wave is ten times upward, fourteen times flat, four times diphasic (− +), five times downward and flat; only three times is the Q wave pattern associated with that downward T wave.

In V_E, the QRS deflection assumes the rS, RS, or Rs pattern; Q or QS waves are never met; the S-T segment lies fourteen times on the base line, nineteen times above it as in the right precordial leads. The T wave is usually upward; it appears twice flat, once diphasic and once downward.

In V_{EO}, the QRS deflection shows an rS, RS, Rs or R pattern; no distinct Q or QS wave has been met; the T wave usually upward is five times flat.

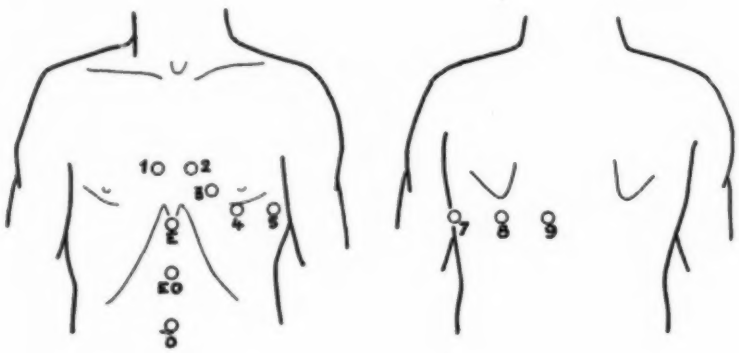

Fig. 1.—Location of the points *7*, *8*, *9*, *E*, *EO* and *O* from which additional unipolar leads are taken.

In V_O, the QRS deflection seldom shows an rS or RS pattern (four times); usually exhibits a Rs or R pattern. There is no QS or Q wave to be seen. The T wave is usually upward; it is six times flat, never downward. In twenty-seven cases, the features of the ventricular complexes are the same as in Lead aV_F. In thirteen of those cases, they are the same as in Lead III. Thus, in six cases, the features of the ventricular complexes are different from those of Leads aV_F and III. In fourteen cases only are they different from those met in Lead III.

In V_{EO} and V_O, the S-T segment lies twenty-six times on the base line, is five times slightly depressed, and only twice elevated. As a general rule, the ventricular complexes show different features in V_E on one side, in V_{EO} and V_O on the other side.

It will be noted that in this series of tracings of normal subjects, the electrocardiographic position of the heart was five times vertical, seven times semivertical, eighteen times intermediate, three times semihorizontal. Since no horizontal position has been met, those data do not exclude the possibility of finding a Q or QS wave as a normal variant in V_{EO} and V_O.

REMARKS

1. The question as to whether the additional unipolar leads studied are near or remote leads will not be discussed in this report, our aim being essentially practical. We are aware that the majority of those leads do not assume the character of near unipolar leads.

2. The extension of the investigations on the chest wall remains complicated by the presence on the right side of QS patterns and on the left back side of QR patterns, the location of which may vary normally to a certain extent, according to the position of the heart (Simonson[18]). It should be noted on the other hand that the patterns of infarction in esophageal leads at the ventricular level and in gastric leads are also submitted to limitations (Kistin and associates[10]). This is the reason that, especially in the back Leads V_8 and V_9, only characteristic changes of both S-T segment and T wave (dome shaped S-T, coronary T wave of Pardee, cove-plane T wave), usually with the presence of a characteristic Q wave pattern, were taken under consideration.

3. We are aware that the additional unipolar leads used cannot in a better way than the others give reliable information on the true anatomical location of an infarct. The object of this study is to make the diagnosis of coronary thrombosis easier by additional information and chiefly to ascertain more precisely the location and extension of the infarct related to the different planes of the thorax, whatever the position of the heart in it. However, mention of the position of the heart will generally be made, according to the needs of the report.

RESULTS

Infarctions of the Anterior Group (Figs. 2, 3, 4, 5, and 6).—

In anterior, usually extensive, infarction, Lead V_E shows direct infarction patterns in sixteen out of the eighteen cases studied in this lead, whatever the location and extension of the infarcts. The reason it shows no changes in two cases is not apparent. In anteroseptal infarction, six out of seven cases show direct infarction patterns; the seventh case is an old infarct, the electrocardiographic changes of which had much regressed in the routine leads. In anterolateral infarction, Lead V_E does not exhibit any pathological features in eleven out of twelve cases. A single case where the infarct spreads more distinctly on the anterior wall shows infarction patterns in V_E.

The appearance of direct patterns in V_E in the anterior infarctions does not seem to depend on the electrocardiographic position of the heart. In the majority of our cases, the position was horizontal, though also semihorizontal and intermediate. Four times, a semivertical or vertical position has been met. Lead V_E has shown direct infarction patterns in these cases as well as in the others. No attempt was made in fact to modify the position of the heart by deep breathing.

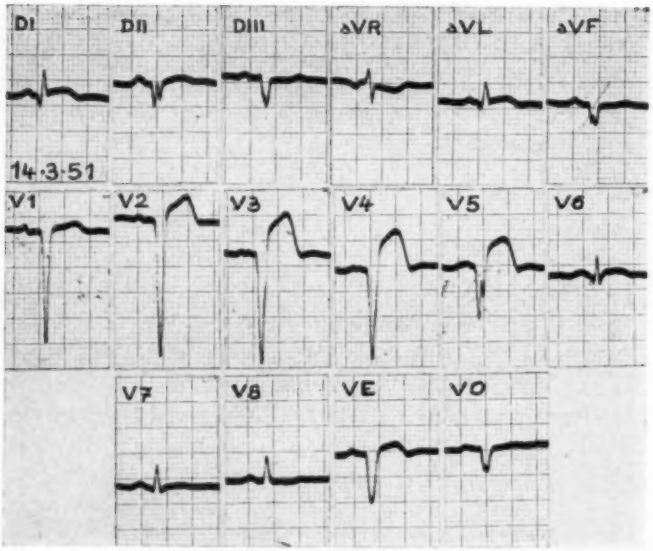

Fig. 2.—A 50-year-old man. Extensive anterior infarct, 8 days after the coronary accident. Positional QS wave in aV_F. Reciprocal changes of infarction are already present in V_8. V_E displays direct infarction patterns. V_O is similar to aV_F. Heart in horizontal position.

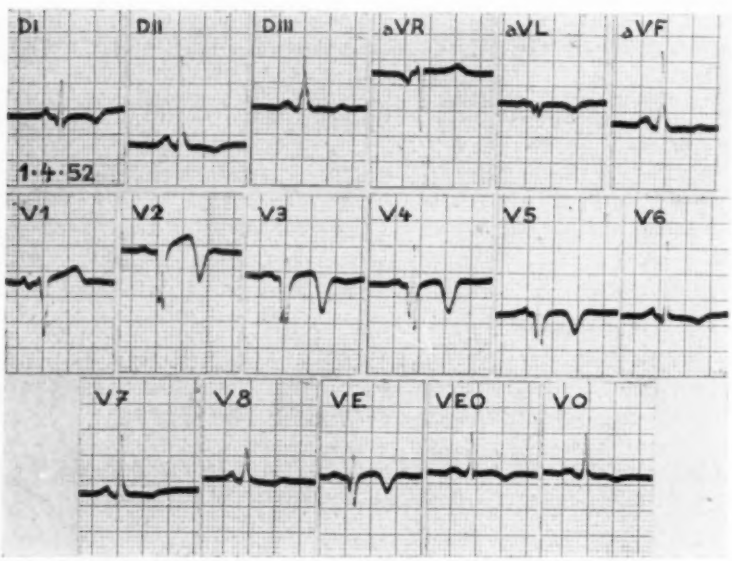

Fig. 3.—A 61-year-old man. Rather extensive anterior infarct, 8 days after the coronary accident. This does not involve the lateral wall to a large extent (reciprocal changes in V_7 and V_8). V_E shows characteristic infarction patterns; the changes are less complete and distinct in V_{EO} and V_O, but Lead aV_F does not exhibit any infarction features. Heart in semivertical position.

Leads V_{EO} and V_O exhibit features that generally differ from those shown in V_E. Fourteen cases of the anterior, more or less extensive infarctions, all recorded in V_E, have been recorded in these leads. Three cases show infarction patterns in V_{EO} and V_O, much less characteristic than in V_E (Fig. 3). Four other cases display a QS wave, without other patterns, either in V_{EO} only or both in V_{EO} and V_O and, simultaneously, three of them show a QS wave and the fourth a Q wave in Leads III and aV_F (Fig. 2). This QS wave is due once to an old posterior myocardial lesion and seems to be due twice to the position of the heart. The seven remaining cases do not exhibit any abnormal pattern in V_{EO} and V_O.

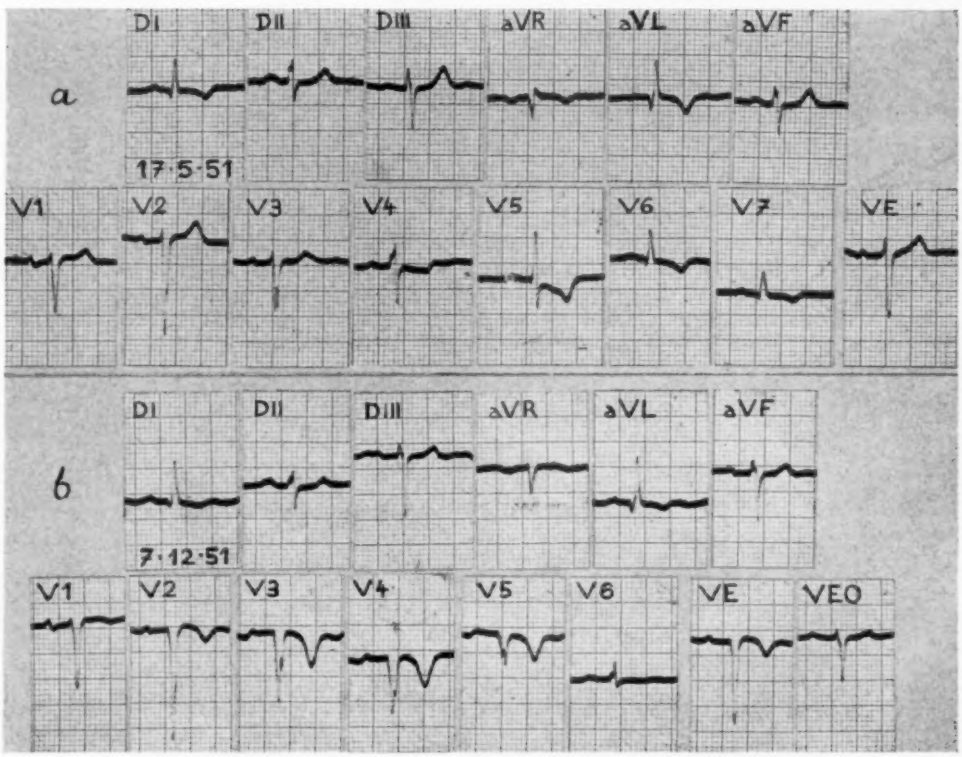

Fig. 4.—A 73-year-old man. *a*. 3-month-old anterolateral infarct; the electrocardiogram was characteristic one month after the coronary accident. Less typical changes remained in Leads I, aV_L and the left precordial leads up to V_7. V_E is silent. Heart in horizontal position. *b*. Rather extensive anterior infarct occurred 6½ months later; tracings recorded 6 weeks after the coronary accident. V_6 does not show any more changes of the old infarct. V_E displays typical infarction patterns. V_{EO} is silent. Heart remained in horizontal position.

Six of the seven cases of anteroseptal infarction recorded in V_E are recorded in V_{EO}. In this lead, one case shows a QS pattern, a second displays direct infarction patterns, but less characteristic than in V_E; there are no corresponding anomalies in aV_F. Five cases are recorded in V_O; a single one shows a broad Q wave which exists in Leads III and aV_F and is the remnant of an old posterior lesion. Both V_{EO} and V_O are silent in the other cases.

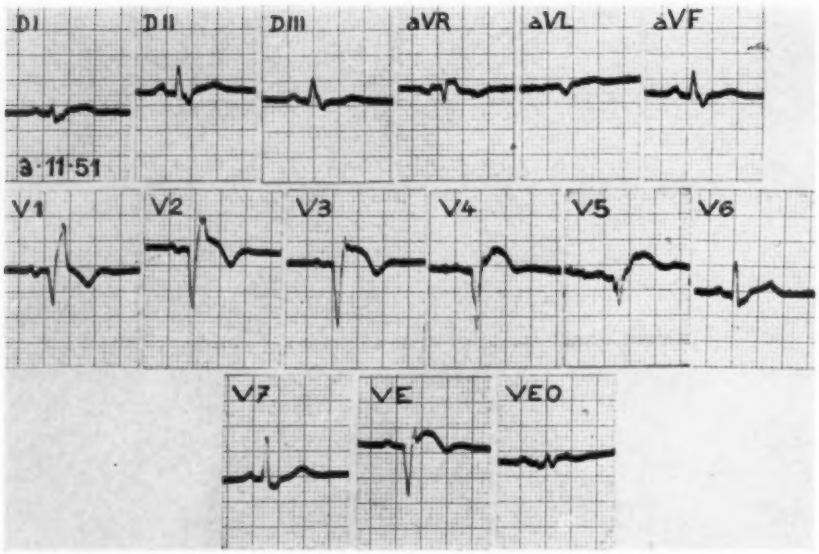

Fig. 5.—A 67-year-old man. 8-day-old anteroseptal infarct complicated by transient right bundle branch block. Characteristic infarction patterns in V_E. V_{EO} shows less distinct patterns but its features are quite different from that of aV_F. Heart in semivertical position.

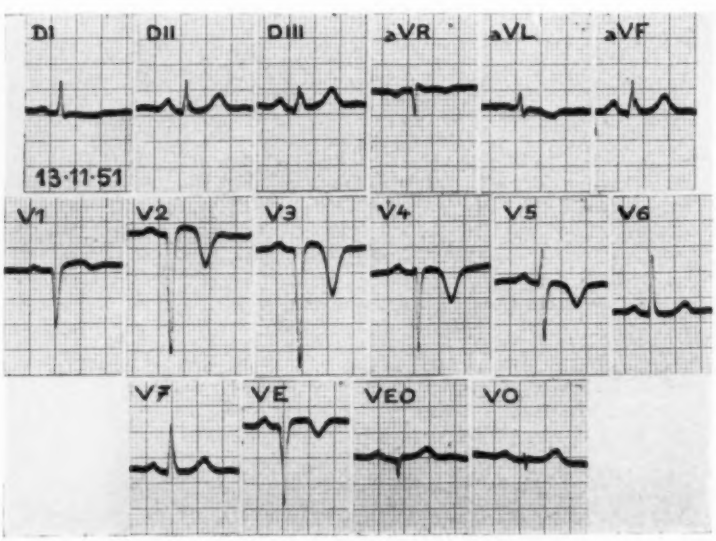

Fig. 6.—A 58-year-old man. Anteroseptal infarct, 5 weeks after the coronary accident. Direct infarction patterns in V_E, disappearing in V_{EO} and V_O. QS wave in V_{EO}. Leads V_{EO} and V_O show features that are different from those met in aV_F. Heart in intermediate position.

In conclusion, these high abdominal leads seldom yield direct infarction patterns, moreover, they are less characteristic than in V_E, in the anterior and anteroseptal infarcts in which they have been recorded. On the other hand, they may display a positional QS wave or a Q or QS wave deriving from a coexisting old posterior myocardial lesion and, in both cases, the same waves are generally found in Leads III and aV_F.

In the anterolateral infarction, Lead V_{EO} shows no infarction pattern in eight out of nine cases studied; nor does the V_O in six of seven cases. Thus a single case, the same which displayed characteristic changes in V_E, shows infarction pattern in V_{EO} and V_O. This case has previously exhibited posterior infarction patterns of which there remain changes in Leads III and aV_F analogous to those recorded in V_{EO} and V_O.

Lead V_7 has been recorded in the twenty cases of the anterior, more or less extensive, infarctions. It shows direct features of infarction in seven cases, indicating the lateral extension of the infarcts. V_8 shows once a large spreading of an extensive anterior infarct to the lateral wall of the left ventricle. In no case have the changes spread to V_9. In eight cases, on the other hand, there are reciprocal changes of infarction in V_7, V_8 and V_9.

These lateroposterior leads are, as one may expect, constantly silent in the anteroseptal infarcts.

In the twelve cases of anterolateral infarction, direct infarction patterns spread frequently to V_7 (8 cases); three times they spread to V_8 and even once to V_9.

Infarctions of the Posterior Group.—

Plain posterior infarction (Figs. 7, 8, and 9): In twenty-two out of the twenty-seven cases recorded, Lead V_E either is silent or shows, as the routine precordial leads, reciprocal changes of infarction (10 cases) consisting of a depression of the S-T segment or an exaggeration and symmetrical pattern of the T wave. It displays direct infarction patterns in five cases. One of these exhibits a spreading of the posterior infarct to the lateral wall. In three others, the characteristic features appear in V_E only when the posterior infarct becomes posterolateral in the course of its evolution. In a fifth case, a QS pattern, probably due to the position of the heart, took place in V_E after a long time without other characteristic features in that lead.

In opposition to the usual opinion,[7,19] the heart is most often in horizontal or intermediate position in our cases of plain posterior infarction. In five cases only, the heart is in vertical or semivertical position. In the cases showing direct infarction patterns in V_E, the heart is twice in vertical position, twice in intermediate position, and once in horizontal position.

The high abdominal Leads V_{EO} and V_O show direct infarction patterns in nineteen out of the twenty-six posterior infarcts recorded in these leads. It is the reverse of what happens in V_E. It will be noted that the cases which show direct infarction patterns in V_E, exhibit them in V_{EO} and V_O as well. But in these cases, the patterns are more distinct, characteristic and complete in V_{EO} and V_O than in V_E. In one case, the electrocardiographic features become progressively more characteristic as the exploring electrode is carried from V_E to V_{EO} and then to V_O.

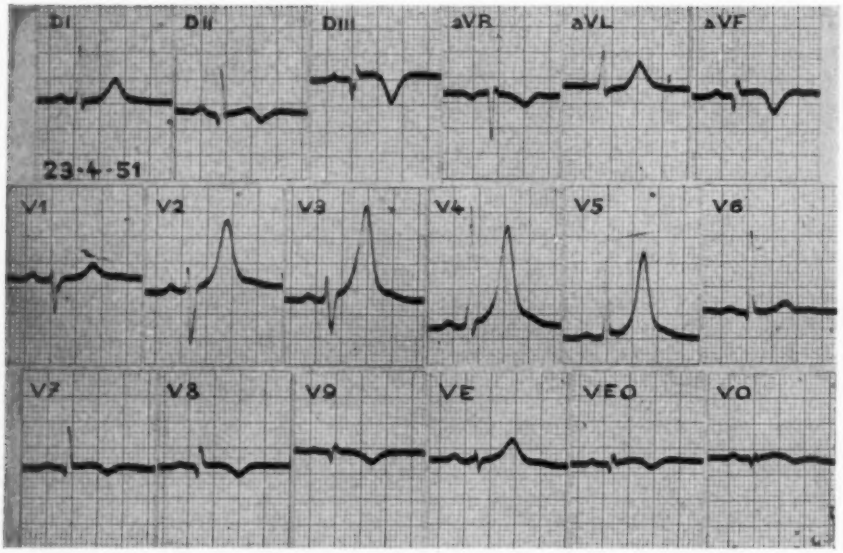

Fig. 7.—A 46-year-old man. Plain posterior infarct, 15 days after the coronary accident. Reciprocal changes of infarction are present in the precordial leads from V_2 to V_5. V_E shows reciprocal changes too. Direct infarction patterns are present in the dorsal unipolar Leads V_7, V_8, and V_9 and in the Leads V_{EO} and V_O located lower than V_E. Heart in intermediate position.

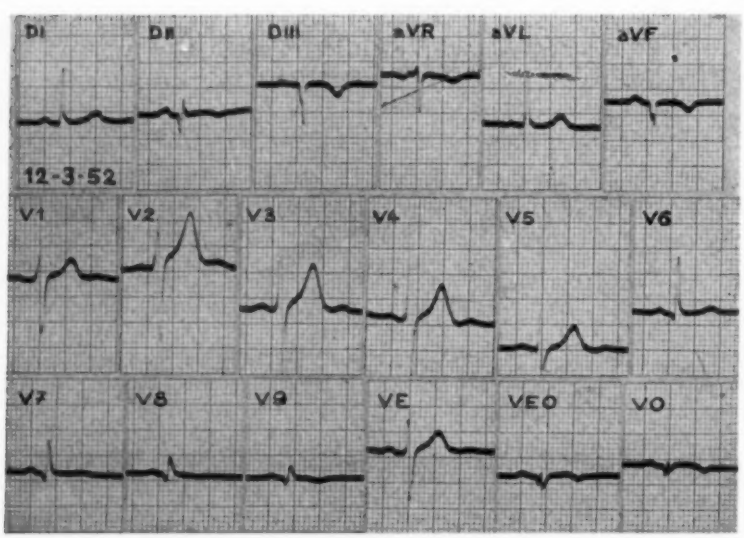

Fig. 8.—A 50-year-old man. 5-month-old plain posterior infarct; the electrocardiogram was characteristic in the first days following its onset. The direct infarction patterns show a tendency to regress in Leads III and aV_F. The unipolar dorsal leads are not characteristic. V_E is silent. But the high abdominal leads V_{EO} and V_O still display striking direct infarction patterns. V_{EO} and V_O show features that are quite different from those met in aV_F. Heart in horizontal position.

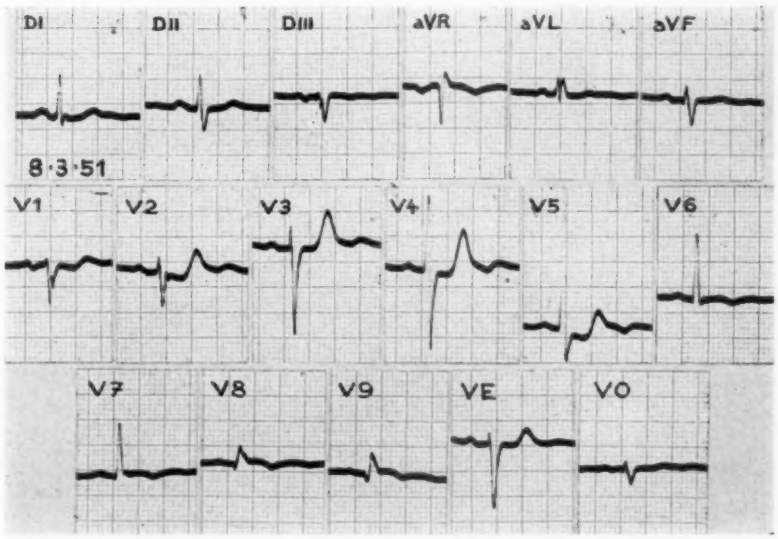

Fig. 9.—A 70-year-old woman. The patient has suffered, respectively, 2½ years and 1½ years previously, two attacks of posterior infarction that were tested repeatedly by electrocardiograms and no features of which are left in Leads III and aV_F. V_E and V_O are silent. But the dorsal unipolar Leads V_7, V_8 and V_9 still show direct patterns of the lesion. Heart in horizontal position.

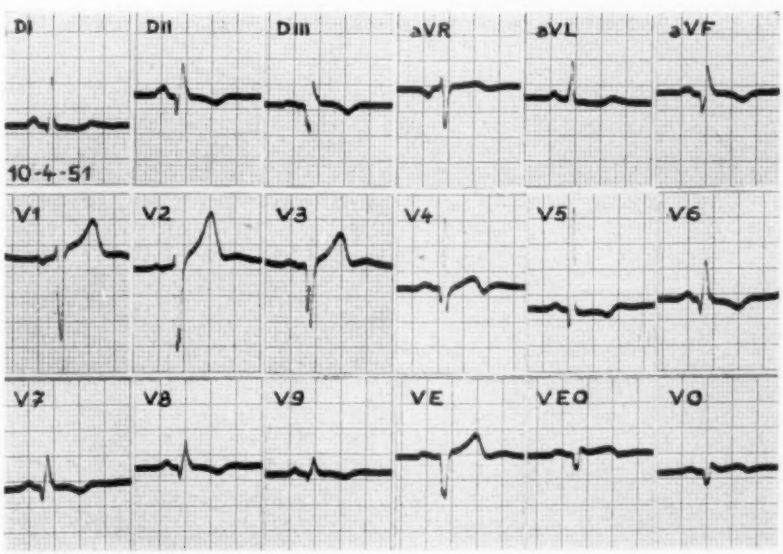

Fig. 10.—A 63-year-old man. Fifteen-month-old posterolateral infarct, the electrocardiographic patterns of which have not changed for the last 9 months. The dorsal unipolar leads show the lateral extension of the infarct. V_E is silent, exhibiting features similar to those of V_1 and V_2. V_{EO} and V_O on the contrary display characteristic direct patterns of the infarct. Heart in intermediate position.

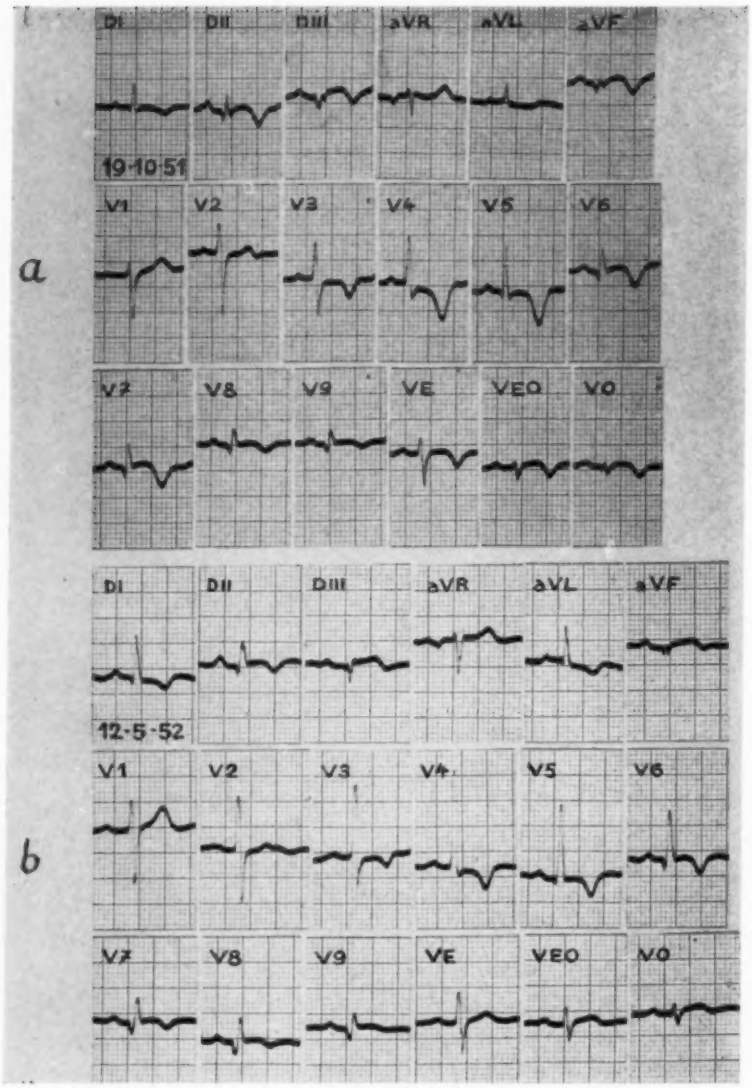

Fig. 11.—A 71-year-old woman. Posterolateral infarct. *a*. Four weeks after the coronary accident. Direct infarction patterns in the dorsal unipolar leads, less characteristic in V_{EO} and V_O, incomplete in V_E, however, this lead shows changes due to the infarct. Heart in semihorizontal position. *b*. Seven months later. The direct patterns have disappeared in V_E, V_{EO} and V_O but remain characteristic in Leads III, aV_F and the dorsal unipolar leads. High abdominal leads do not take the same point of view of the lesion as does aV_F.

The dorsal unipolar Leads V_7, V_8 and V_9 have been recorded in thirty-one of the cases of plain posterior infarction. Direct infarction patterns have been found in eighteen cases in V_7 and V_8. In V_9, eight cases showed characteristic patterns too. The changes could not be mistaken with the pattern Q,T— that may occur normally in this lead.

Direct infarction patterns appear simultaneously in the high abdominal leads and in the unipolar dorsal leads in twelve of twenty-four cases studied in both groups of leads. The position of the heart does not provide the reason why the lesions give rise to changes in both groups of leads or only in one rather than the other group. There is no doubt that it depends on the location and the extension of the infarcts.

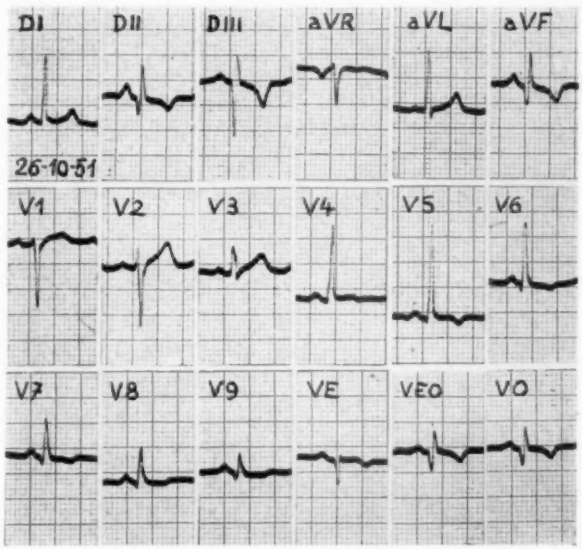

Fig. 12.—A 50-year-old man. Posterolateral infarct nearly 4 years after the coronary accident, the electrocardiographic features of which have not changed for the last 2 years. The signs of the lateral involvement present in V_4 and V_5, already begin to disappear in V_6 and are missing in the dorsal leads; on the contrary, Leads V_E, V_{EO} and V_O show characteristic infarction patterns. The posterior lesion seems to involve the anterior wall by inferior and not by lateral way.

Posterolateral infarction (Figs. 10, 11, and 12): Four out of six cases investigated display direct infarction patterns in V_E. In those four cases, the heart is in horizontal position; it is in, respectively, semihorizontal and intermediate positions, in the two cases which do not exhibit changes in V_E.

The high abdominal Leads V_{EO} and V_O display direct infarction patterns in the same cases where Lead V_E shows them. Once again the features are more distinct and complete in those leads than in V_E. One case, where Lead V_E is silent, displays characteristic infarction patterns in V_{EO} and V_O (Fig. 10).

The unipolar dorsal leads show infarction patterns which spread constantly to V_9 in five of seven cases. The two other cases, where the infarction patterns are already less characteristic in V_6 than in V_4 and V_5, do not exhibit any characteristic patterns in the unipolar dorsal leads, whereas they show characteristic features in V_E, V_{EO} and V_O.

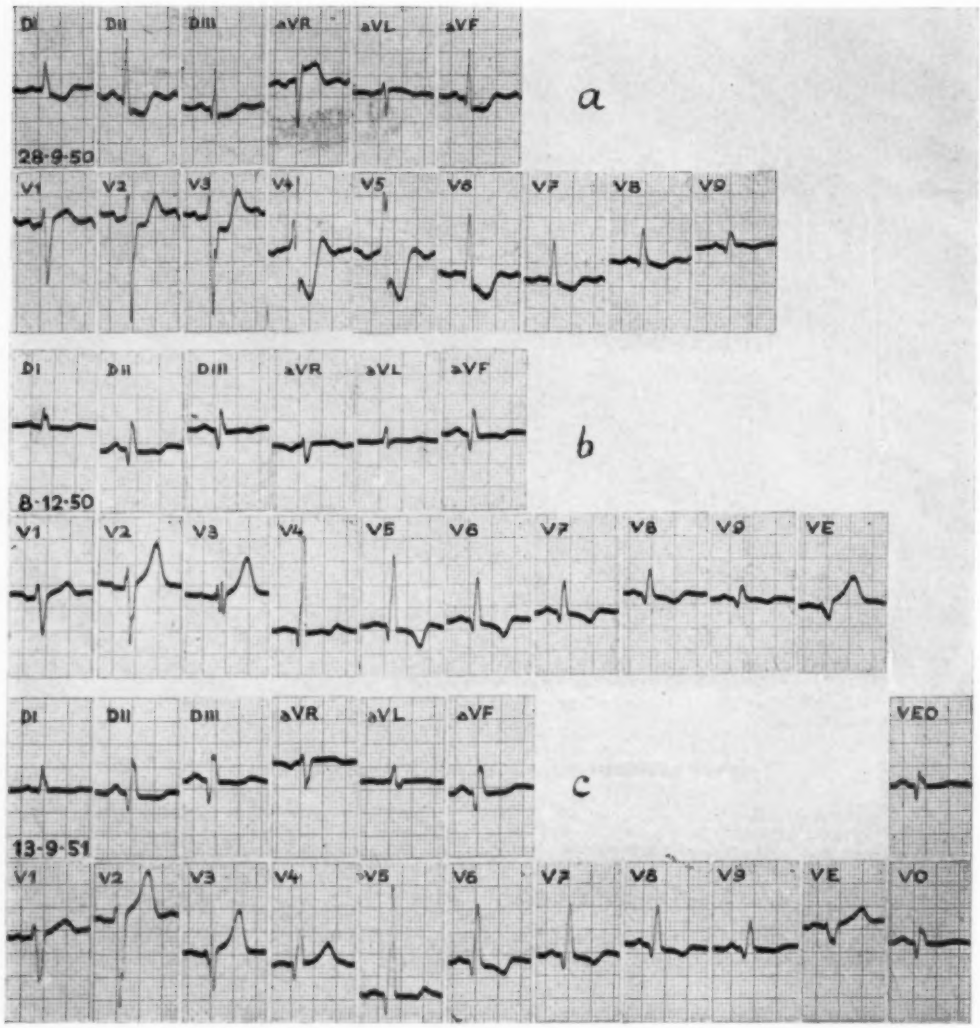

Fig. 13.—A 50-year-old man. Extensive subendocardial infarct, assuming thereafter the features of posterolateral infarction. *a*. Four days after the coronary accident: subendocardial pattern spreading to the full set of the dorsal leads (V_7, V_8, and V_9). Heart in vertical position. *b*. Two and one-half months later: the lesion has assumed the features of a chiefly posterolateral infarction: direct infarction patterns in Leads III, aV_F and from V_5 up to V_9; reciprocal changes in V_2, V_3 and V_E. *c*. Ten months later: V_E still shows reciprocal changes of the infarct: presence of a coronary Q wave in V_{EO} and V_O.

Posteroseptal infarction: Three cases have been recorded in V_E and show direct infarction patterns in this lead; two of the three cases yield, however, more distinct and complete changes in V_{EO} and V_O. These three cases have been recorded in the unipolar dorsal leads; two exhibit obvious direct infarction patterns in V_7, V_8, and V_9.

Infarction Both Anterior and Posterior.—

Lead V_E shows direct infarction pattern in one of two cases recorded in that lead. Leads V_{EO} and V_O on the contrary exhibit characteristic features in these two cases. In the unipolar dorsal leads, one of three cases shows only characteristic changes in V_7, the other two up to V_9.

Subendocardial Infarction.—

One case only is interesting for the present study. It is summed up on Fig. 13.

DISCUSSION

1. *What is the information furnished by the additional unipolar leads?*

a. Lead V_E exhibits direct infarction patterns in nearly all the anterior infarcts recorded, whatever their extension and location; the same is true for the anteroseptal and posteroseptal infarcts studied. To the reverse, V_E is silent in the anterolateral infarcts and in the majority of the plain posterior infarcts where it may show reciprocal changes of infarction. It may display, however, direct infarction patterns when the infarct is posterolateral or when it becomes posterolateral in the course of its evolution. In opposition to the general opinion, Lead V_E gives information on the lesions of the anterior wall of the heart and usually does not furnish any information on the posterior or diaphragmatic wall involvement, except when the lesions spread over the anterior wall.

Soulié and Laham[19] look upon the presence of direct infarction patterns in Lead V_E (V_{E2}) in the anteroseptal infarct as furnishing evidence of a larger extension of it on the anterior and right aspects of the septum. It must be noted in the present study that (1) nearly all anterior and anteroseptal infarcts show direct patterns in V_E; (2) however, the position of the heart in the thorax and consequently the relations of the septum with the thoracic wall may differ very much in the anterior infarcts of various extensions studied. When using the test of septal infarction probability proposed by Myers and associates[13] (coincidence of a QS pattern in V_1, or V_1 and V_2, with an intrinsicoid wave of the right atrium), the probability for the changes occurring in V_E to be caused by a septal involvement would be only 50 per cent of the studied anterior and anteroseptal infarcts. One thing seems to be certain, V_E belongs to the leads that explore the anterior wall of the heart and not to the leads of the diaphragmatic wall.

b. For exploring the posterior and inferior wall of the heart, it is necessary to lead from points lower than V_E, at the level of the high parts of the abdominal wall. The leads that have been chosen at this level, V_{EO} and V_O, usually display direct infarction patterns in the plain posterior infarcts and in the infarcts that are or become posterolateral. In the latter, the features are more characteristic and complete in V_{EO} and V_O than in V_E. It is likely, when V_E shows direct infarction patterns, that the posterolateral infarct spreads over the anterior wall of the heart not only through the lateral wall but also through the inferior wall and perhaps merely by this way in certain cases (Fig. 12), assuming then the features of an anteroinferior lesion; such a location may be due solely to the position of the heart in the thorax. It seems different from the location of the anteroinferior infarction described by Cabrera[3] where a septal involvement appears in the Leads V_1, V_2 and V_3.

The high abdominal Leads V_{EO} and V_O seldom exhibit direct infarction patterns, less characteristic than in V_E, in the group of anterior infarctions, probably indicating that the anterior infarct involves the posterior wall. In some cases they display, as do the Leads III and aV_F, positional QS waves or Q and QS waves indicating the coexistence of old posterior lesions.

The set of leads from V_E to V_O enables one in consequence to assume whether a posterior infarct involves the wall of the heart chiefly on its inferior aspect (V_{EO} and V_O) or even spreads to its anterior aspect (V_E). Conversely, those leads could give information as to whether an anterior infarct spreads over the inferior wall of the heart, even perhaps in the absence of changes in Leads III and aV_F (Figs. 3 and 5). The leads of the thoracic wall lying above V_E and including this lead give information on the lesions of the anterior wall of the heart; those lying lower than V_E on the abdominal wall, on the lesions of the inferoposterior wall. These statements are in agreement with the data expressed by Duchosal and Sulzer,[5] when these authors recorded full sets of leads from V_1 to V_6 at different levels (fourth and sixth intercostal spaces), in cases of posterior infarction and noted that infarction patterns appear only in the set of leads at the level of the sixth intercostal space.

c. Dorsal unipolar Leads V_7, V_8 and V_9 furnish information, the value of which may be more limited. In fact, if a positional QS may appear normally sometimes in the leads from V_E to V_O and up to aV_F, a QR, T— pattern will be more often found in V_9 in normal subjects. We have never seen it in normal subjects in V_8. In the present study only unequivocal infarction patterns have been retained in V_8 and V_9.

Lead V_7, exceptionally V_8, is useful for measuring the grade of extension of an extensive anterior infarct. The same is true for the anterolateral infarcts, in which exceptionally the characteristic patterns extend up to V_9.

The dorsal unipolar leads exhibit direct infarction patterns in half of the posterior infarcts studied, even the V_9 in some of them. This statement is in agreement with that of Meyer and Schmidt[12] concerning V_8 and with the data from the tracings of Herrmann and associates.[9] It concerns probably infarcts of usually posterobasal location. Those leads show characteristic infarction patterns in the majority of the posterolateral infarcts.

To sum up, Leads V_7, V_8 and V_9 may be considered as giving information on the posterolateral location and extension of infarcts, in agreement with the opinion of Myers and associates,[14] corroborating that of Wilson and coworkers.[21]

It is certain that in every case of posterior infarction, the recording of both dorsal unipolar leads and high abdominal leads enables one to know more exactly the location and extension of the infarct.

2. *Are the additional leads studied useful for the electrocardiographic detection of infarcts?*

The group of posterior infarcts is, of course, the most interesting from this point of view. This question cannot be solved here, for the present study has been limited to authenticated cases of infarction, identified in the twelve routine leads. But the late evolution of some cases seems to give an affirmative answer to it, as the infarction patterns persist in the additional leads studied, although they have lost their typical features in the routine leads (Fig. 9).

3. *Are some of the additional leads studied a useless repetition of some routine leads?*

This question deserves consideration. Myers and associates[15] have shown that the leads of the abdominal wall should display patterns analogous to those of the unipolar lead of the left leg (V_F or aV_F). Wolferth and associates,[22] however, believe that the potentials transmitted to the higher parts of the abdominal wall arise in the precordial area and that diaphragmatic potential patterns appear only at lower levels.

It seems that the distribution of the cardiac potentials on the body surface is affected by other components. The present study shows indeed that not seldom do Leads V_{EO} and V_O display patterns which are quite different from those shown in aV_F (Figs. 3, 5, 6, 8, and 11), or that the infarction patterns are missing in this lead, although being present in the high abdominal leads (Figs. 3 and 5) or also the reverse (Fig. 11).

These leads seem to present aspects of the lesion somewhat different from those recorded in Lead aV_F.

SUMMARY

In eighty-eight cases of myocardial infarction, clinically identified, of which the electrocardiographic features were pathognomonic in the standard limb leads, the unipolar limb leads and the six Wilson's unipolar precordial leads, the evolution of two-thirds of which was followed, additional thoracic and abdominal unipolar leads have been studied. These may be divided into three groups: (1) Lead V_E from the ensiform cartilage; (2) two leads on the median abdominal line, one at the level of the umbilicus (V_O), the other at the center of a line joining V_E and V_O, which may be called V_{EO}; and (3) the lateroposterior leads V_7, V_8, and V_9. Every lead has been recorded in thirty-three normal subjects.

The cases of infarction studied may be divided according to their location into: anterior less or more extensive, 20; anteroseptal, 7; anterolateral, 12; plain posterior, 33; posterolateral, 7; posteroseptal, 3; that is, 39 infarctions of the anterior group and 43 of the posterior group; lastly, 4 infarcts both anterior and posterior and 2 subendocardial infarcts.

From this survey, the following conclusions may be drawn:

1. Lead V_E shows direct infarction patterns in nearly all anterior infarcts studied, whatever their location and extension, and in the anteroseptal and posteroseptal infarcts studied. This lead is, on the contrary, silent in the case of anterolateral and posterior infarcts. However, it may show direct patterns when the infarcts are or become posterolateral.

2. The high abdominal Leads V_{EO} and V_O usually show direct patterns of infarction, not only in the plain posterior infarcts, Lead V_E remaining silent, but also in cases of infarcts which are or become posterolateral. In the latter, the features in V_{EO} and V_O are more characteristic and complete than in V_E. Leads V_{EO} and V_O are often silent in the cases of anterior, anteroseptal, or anterolateral infarction.

3. Lead V_7 may be useful for measuring the extent of a large anterior infarct, the features of which may spread exceptionally to V_8. The same conditions are true in the case of anterolateral infarcts that may show infarction patterns up to V_9. Leads V_7, V_8, and V_9 often show direct infarction patterns in the cases of plain posterior infarction and of posterolateral infarction.

By leading from V_E, V_{EO} and V_O, it is possible to know whether a posterior infarct involves chiefly the inferior wall of the heart (V_{EO} and V_O) or spreads to its anterior wall (V_E) and, reciprocally, it would be possible to know if an anterior infarct (V_E) spreads over the inferior wall (V_{EO} and V_O). The unipolar dorsal Leads V_7, V_8, and V_9 give information on the lateral and posterior location and extension of the infarcts.

Lead V_E seems to belong to the group of leads that explore the anterior wall of the left ventricle and the septum. Usually, it does not furnish information about the lesions of the posterior or inferior wall which give rise to characteristic changes at lower lead points at the level of the abdominal wall. Leads V_7, V_8, and V_9 are useful for exploring the posterior wall, and more especially the posterolateral wall, of the left ventricle.

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FUNCTIONAL ANATOMY AND "THROTTLE VALVE" ACTION OF THE PULMONARY VEINS

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ALTHOUGH many publications have appeared concerning the mechanism of acute pulmonary edema,[1-15] few suggest the possibility that constriction of the pulmonary veins may produce this condition.[14,15] However, the existence of this phenomenon is suggested by certain observations in man and other animals, especially in the presence of disturbances of the central nervous system.[11,13,16] One is prone to attribute acute pulmonary edema to acute failure of the left ventricle, although it is possible that the subject may at times be manifesting acute spasm of the pulmonary veins. This venous spasm may be related to antigen-antibody or hypersensitivity reactions or to reflex autonomic stimulation.

As a rule, the therapy employed in the management of acute pulmonary edema is directed at acute left ventricular heart failure. Such measures as the use of atropine, oxygen, digitalis preparations, bed rest and morphine might reduce venous tone either directly or indirectly if venous spasm were present, and the results might be attributed to cardiac effects. This is true because one's attention and therapeutic objectives are directed primarily at the heart, and the other effects of the therapeutic measures are often overlooked.

When it is remembered that as much blood traverses the cross sectional area of the four pulmonary veins at low levels of pressure as that of the aorta per unit of time, it becomes apparent that the degree of patency of the pulmonary veins would significantly influence the volume of blood which may enter the left ventricle per unit of time to be ejected. In fact, it has been suggested[16] that the pulmonary veins possess a throttle action. This throttle valve action could determine cardiac output. As indicated elsewhere,[17] an obstruction to blood flow into the left ventricle may result in rapid and serious congestion of the vessels of the lungs with blood, producing acute pulmonary edema or acute left ventricular failure. It is known that the pulmonary veins have a considerable amount of smooth muscle within their walls and a rich supply of autonomic nerves. In addition, the blood pressure within the pulmonary veins is relatively low and might be overcome by a small force of contraction to reduce the size of the venous lumen.

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Because of the probable importance of the pulmonary veins in the regulation of pulmonary blood flow and the possibility of spasm of the pulmonary veins as a cause of acute pulmonary edema, studies of the anatomic nature of the junction of the pulmonary veins with the left atrium seemed desirable.

MATERIALS AND METHODS

The lungs and hearts of five patients were obtained at autopsy within three hours after death. The four pulmonary veins were cut transversely as far out into the lungs as they could be followed. The left atrium was removed carefully from the remainder of the heart by cutting it away from the left ventricle at the atrioventricular groove. The junction of the pulmonary veins with the left atrium was not disturbed. After the pulmonary veins and left atrium were removed, strips, 3 to 5 mm. wide and 35 to 40 mm. long, were cut, beginning from the severed end of the pulmonary vein within the lung and continuing well into the left atrial wall. The strips represented longitudinal segments of vein and segments of left atrium, including the junctional area. Sections from the anterior and posterior walls of each of the four pulmonary veins, or eight specimens for each subject, were obtained.

The strips were fixed in formalin, sectioned longitudinally, and stained with Mallory's trichrome stain for muscle. Some preparations were also stained with hematoxylin and eosin. Each section was studied microscopically, and diagrams were made of each to indicate the extent and nature of distribution of smooth and striated muscle. The distance and nature of overlap of the two types of muscle were determined.

RESULTS

Results of these studies are summarized in Table I and in Figs. 1 through 4.

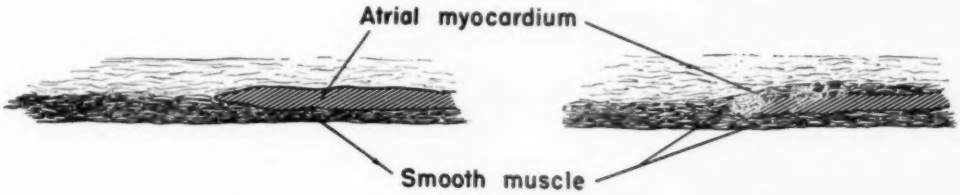
1. *Distance of Overlap of Smooth Muscle and Atrial Myocardium.*—Because of the nature of some of the preparations, it was not always possible to estimate the degree of overlapping of the smooth muscle and atrial myocardium. The mean distance of overlap of the smooth muscle of the venous wall and of the atrial myocardium was 7.6 mm., with extremes of 4 and 17.0 + mm. Variations among the different veins are shown in Table I. The extent of the overlap could not be estimated in most instances with absolute accuracy because the smooth muscle fibers did not end abruptly. The number of fibers gradually decreased, and in some instances smooth muscle extended loosely dispersed in the subendocardial layer of the atrial wall for several centimeters. In most instances and for purposes of analysis the smooth muscle was considered to end where the dense mass of muscle forming the venous wall ended or the smooth muscle fibers definitely became less compact and were loosely scattered in the subendocardial layer. Incidentally, the endothelial layer of the veins continue uninterruptedly as the endocardium and form a continuous one-cell layer lining the veins and left atrium.

TABLE I. SUMMARY OF CLINICAL DATA OF SUBJECTS STUDIED AND DISTANCE IN MILLIMETERS OF OVERLAPPING OF LEFT ATRIAL MUSCLE AND SMOOTH MUSCLE OF THE PULMONARY VEINS

PATIENT NO.	SEX	COLOR	AGE (YR.)	DIAGNOSIS	DEGREE OF OVERLAP OF SMOOTH MUSCLE AND STRIATED ATRIAL MUSCLE (MM.)								
					LEFT SUPERIOR		LEFT INFERIOR		RIGHT SUPERIOR		RIGHT INFERIOR		ALL VEINS
					ANT.	POST.	ANT.	POST.	ANT.	POST.	ANT.	POST.	
1	M	C	56	Gastric carcinoma, liver metastases	5	6	7.5	–	6	4.5	–	4	
2	F	C	14	Ruptured aneurysm, circle of Willis	10+	–	–	–	–	–	–	–	
3	F	W	44	Duodenal ulcer, exsanguination	–	7.5+	10+	–	10	–	–	4.5	
4	F	C	24	Acute vaginal hemorrhage	–	–	–	–	–	–	5	–	
5	M	C	41	Hypertension, uremia, thrombosis, anterior spinal artery	8	–	17+	5+	–	–	11+	–	
				Maximal overlap	10+	7.5	17+	5+	10	4.5	11+	4.5	17+
				Minimal overlap	5	6	7.5	5+	6	4.5	5	4	4
				Mean overlap	7.7	6.7	11.5	5+	8	4.5	8	4.3	7.6

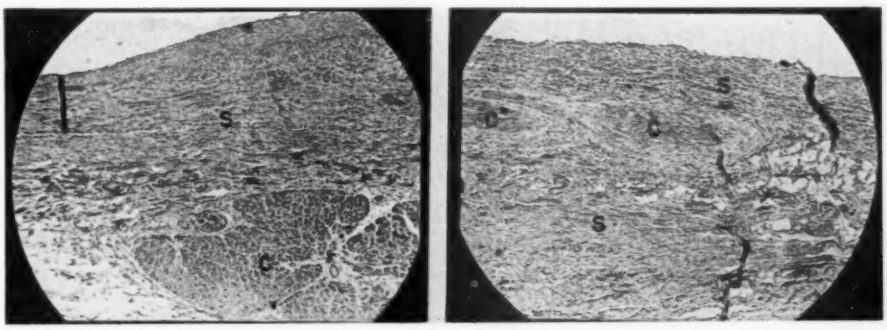
2. *Nature of Overlap of Smooth Muscle and Atrial Myocardium.*—The two types of muscle were found to overlap in two ways in the atriovenous junctions studied. Except for one instance, there was a simple overlap of the atrial myocardium over and external to the smooth muscle of the vein (Figs. 1, *A* and 2, *A*).

The second type of overlap was wedge-shaped, in that the atrial myocardium wedged into the smooth muscle layer of the venous wall, being surrounded on both sides with smooth muscle (Figs. 1, *B* and 2, *B*). This occurred in only one instance and was not an artifact due to sectioning or preparation.



A. *B.*

Fig. 1.—Section of junctions of pulmonary veins with atrium. Diagram showing the nature of the overlap at the left atrium-pulmonary vein junction. *A* represents the usual type of overlap. The smooth muscle of the vein courses between the atrial myocardium and endocardium. The endothelial lining of the veins is continuous with the endocardium. *B* shows the overlap noted in one case in which the smooth muscle of the vein split to enclose the atrial myocardium on both the endocardial and epicardial surfaces.



A. *B.*

Fig. 2.—Photomicrograph of junctions of pulmonary veins with atrium. Longitudinal sections taken at the left atrium-pulmonary vein junction showing the two types of overlap of the atrial sheath. S indicates smooth muscle layer of the pulmonary vein, and *C* indicates striated muscle of the atrium. Sections *A* and *B* correspond to the A and B, respectively, of the two types of overlap shown in Fig 1.

The striated muscle of the atrial myocardium ended sharply in every instance, regardless of the nature of the overlap. The location of its termination was identified without difficulty in all preparations.

3. *Gross Appearance of the Atriovenous Junction.*—The atrial myocardium seemed to extend onto the pulmonary veins for about 10 mm., as observed grossly. This formed a sleeve of myocardium which enclosed the proximal portions of the pulmonary veins (Fig. 3).

Atrial myocardium was seen, microscopically, to extend to within 5 mm. of the first detectable pulmonary alveolar tissue in the preparation. In most in-

stances, it was not possible to measure this distance accurately, because during preparation of the section, pulmonary tissue had been stripped away from the vein.

4. *Nature of Termination of the Lumina of the Pulmonary Veins into the Left Atrium.*—In four of the five subjects studied, the pulmonary veins tended to run perpendicularly into the surface of the atrium as indicated in Fig. 4, *A*. In one instance they entered the atrium obliquely. The superior right and left veins

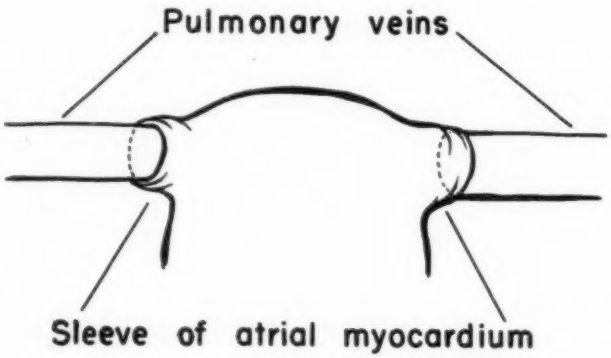


Fig. 3.—Junction of two pulmonary veins with atrium. Diagrammatic sketch of the left atrium and proximal pulmonary veins showing the sleeve of atrial myocardium which invests the proximal portion of the veins.

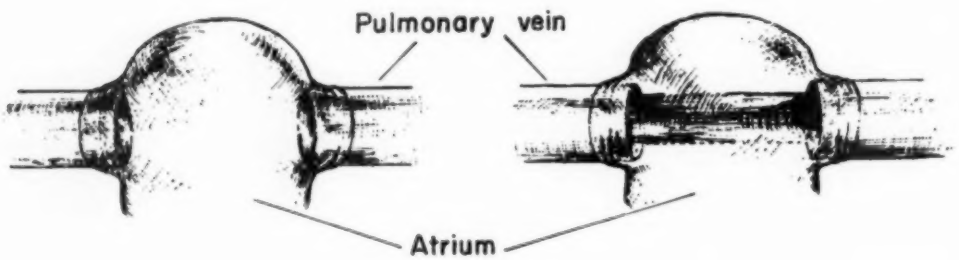


Fig. 4.—Diagram showing two types of portals of entrance of the pulmonary veins into the left atrium. *A* shows the two superior veins opening separately and bluntly at each end of the veins; *B* shows the two superior veins opening at their sides, tending to produce a large single oval orifice at the postero-superior portion of the left atrium.

tended to course directly toward each other and the inferior right and left veins directly toward each other. The orifice through which the blood gained entrance into the atrium appeared to be a more or less lateral opening in the veins. The myocardium overlapped behind this venous tube and extended laterally over them, as indicated diagrammatically by Fig. 4, *B*.

5. *Nervous Tissue in the Pulmonary Veins.*—Although no special staining for nervous tissue was made in these sections, many nerve fibers were found distributed throughout the walls of the pulmonary veins.

DISCUSSION

The anatomic nature of the junction between the pulmonary veins and the left atrium has received little attention by physicians, although it has been repeatedly studied by others.[18-27] This is probably due to the tendency to consider the pulmonary veins as inactive tubes which passively transmit blood from the capillaries of the lungs to the left atrium. This impression of inactivity of the pulmonary veins must be erroneous and, therefore, the functional anatomy of the pulmonary veins should command more attention if pulmonary hemodynamics are to be more adequately understood. Also the pulmonary venous system needs more physiologic study. In the past there has been failure to consider adequately the abundance of smooth muscle in the walls of the pulmonary veins and of their rich supply of autonomic nerves.

As long ago as 1877, Stieda[18] described what he termed an "atrial sheath" in the proximal portion of the pulmonary veins of several animal species as well as of man. According to this author, the presence of striated muscle in the pulmonary venous wall, although not generally recognized, had been noted as early as 1836 by Rauschel.[19] Arnstein[20] in 1877 found the same thing in rats and mice and suggested that this myocardial sleeve structure might have some special functional significance.

More recently several authors have studied the histology of the pulmonary veins in detail in a number of animal species. Takino[21,22] divided various animals into three categories according to the extent of invasion of striated muscle into their pulmonary veins. In the group with the greatest invasion were the rat and mouse and in that with the least invasion were the dog and cat. He found a rich supply of ganglionic cells and nerve fibers in the pulmonary venous walls. He stated that the histologic structure of the pulmonary veins in man is such that they could contract and "throttle the blood stream."

Amano[23] examined post-mortem material from twenty-four Japanese, including two fetuses. To determine the degree of invasion of the pulmonary venous wall by striated muscle, he measured the distance from the distal end of the striated muscle to the pericardial reflection upon the venous wall. This termination occurred from 7.3 mm. proximal to 15.8 mm. distal to the pericardial reflection. Thus, in the majority of instances the striated muscle extended beyond the pericardium to invade the venous wall. In the two fetuses the atrial muscle extended beyond the hilum into the lung. Amano concluded that the proximal portions of the pulmonary veins probably have a sphincter action.

Otterbach[25] extensively studied the histology and embryology of the atrial sheath of the pulmonary veins and proposed that their constricting action prevents reflux of blood into the lungs during atrial systole. This same conclusion was reached by Bucciante[27] in a study of human material. He also found striated muscle to be present in all of twenty-two veins sectioned 5 mm. distal to the atrial orifice.

Physiologic studies showing the contractibility of the pulmonary veins have included lung perfusion experiments as well as plethysmographic studies of the

volume change of isolated strips of vein from both animal and autopsied human sources.[28,29] In fact, contraction has been induced by several pharmacologic agents, including Adrenalin and acetylcholine.

It is evident that the pulmonary veins possess a structure which makes possible variations in their size. The manner and degree with which they vary their luminal size and influence the rate of blood flow from the lungs into the left atrium remain unknown. This possible "throttle" function, which might control the output of the left ventricle by varying the rate of inflow, is an intriguing one which must be evaluated eventually. It may be important in varying cardiac output in normal man so that he can cope with various physiologic circumstances demanding changes in cardiac output. This function must act smoothly in normal people, but it is possible that abnormal or diseased states may be associated with a disturbance in pulmonary venous function so that the "throttle valve" functions abnormally and roughly with overshooting. For example, anaphylactic shock due to reaction to foreign proteins may be associated with excessive spasm of the pulmonary veins, sudden congestion of the pulmonary capillaries, increased hydrostatic pressure, and, in turn, pulmonary edema. The same sequence of events may occur to a varying degree with central nervous system lesions. The acute pulmonary edema described in the several papers reported recently by Sarnoff and associates[11,12,13] in central nervous system lesions may be due in part, at least, to reflex spasm of the pulmonary veins and not only to increase in capillary permeability or failure of the left ventricle. The excellent studies of Aviado and Schmidt[14] suggest that the acute pulmonary edema produced in animals by inhalation of steam is due largely to constriction of the pulmonary veins. Certainly their findings could be explained by venous spasm.

It is interesting even to suggest the possibility of syncope or death from sudden closure of the pulmonary veins by severe spasm which reduces the flow of blood into the left atrium almost to zero and, in turn, the output of the ventricle to the same low level. This might occur so suddenly, with immediate death, that pulmonary edema would not have time to develop. Obviously, varying degrees of interference with output of the left ventricle for varying lengths of time could occur from a dysfunction of the "throttle valve" action of the pulmonary veins.

It is evident that therapeutic agents which dilate veins should improve clinical states due to excessive constriction of the pulmonary veins. In fact, as mentioned previously, the therapeutic measures employed in the management of acute pulmonary edema may owe their beneficial effect to dilatation of constricted pulmonary veins. The use of the potent vasodilators presently available may be of value in patients with acute pulmonary edema without definite evidence of left ventricular failure.

The acute pulmonary edema or congestion in clinical states associated with reflex vasoconstriction of pulmonary vessels, such as in pulmonary embolism and coronary occlusion, may be due to spasm of the pulmonary veins in many instances and not to sudden failure of the left ventricle. The clinical importance of settling this point is evident at the therapeutic level, inasmuch as the present approach in management may not be as satisfactory as it could be.

Aspects of hemodynamic influence of the size of the lumina of pulmonary veins upon the blood flow are evident from a discussion reported elsewhere.[17] There is need for direct study of such phenomena. This paper has indicated several physiologic problems which await study of the pulmonary veins, a segment of the circulation long neglected. Through the four pulmonary veins flows as much blood as through the aorta. It flows through these veins at a low pressure and in lumina which can vary in size. It is evident that these veins may control the cardiac output under certain circumstances and may influence the output regularly.

The sleeve of atrial myocardium which encloses the terminal portions of each of the four pulmonary veins probably serves as a valve to prevent excessive regurgitation of blood into the pulmonary veins during atrial systole. Since the area of atrial myocardium in the vicinity of the orifices of the pulmonary veins is activated first, the myocardium in this area must contract first during systole of the left atrium. This would squeeze upon the pulmonary veins, reducing their luminal size or possibly even closing them before the atrium undergoes final and vigorous contraction. This would tend to reduce or prevent regurgitation of blood into the pulmonary veins and insure forward flow into the left ventricle.

It is interesting to speculate on the possible role of this sleeve of atrial myocardium in preventing closure of the orifice of the pulmonary veins for a prolonged period of time. Since cardiac muscle does not develop tetanic contraction, this atrial sleeve surrounding the proximal portions of the pulmonary veins could not under usual circumstances undergo sustained contraction. Therefore, the atrial muscle could not close the terminal portions or orifices of the pulmonary veins except for a brief period during systole of the atria. Of course, as indicated previously, the smooth muscle of the pulmonary veins could develop tetanic contraction for a sufficiently long period of time to produce serious disturbances in pulmonary blood flow and cardiac output.

SUMMARY

The functional anatomy of the junction of pulmonary veins and atrium has been studied, and the findings have been presented. The probable significance of the anatomy of this region in cardiac and pulmonary hemodynamics in health and disease has been indicated. The possible role of the "throttle valve" action of pulmonary veins in acute pulmonary edema, syncope, and sudden death, as well as its therapeutic implications, has been discussed.

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STUDIES ON WHOLE BLOOD AND MUSCLE CREATINE LEVELS: EFFECT OF SYSTEMIC AND LOCAL ANOXIA, OF CARDIAC FAILURE AND COMPENSATION, AND OF ALPHA-TOCOPHEROL ADMINISTRATION

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PHOSPHOCREATINE is an essential component of the chemical reactions which produce muscle contraction. This compound is very labile and separates into phosphoric acid and creatine in equal molar parts when muscle is stimulated. A one-to-one quantitative relationship between phosphorus and creatine content has been established by Fiske and Subbarrow.[1] The recovery of muscle excitability depends upon the resynthesis of phosphocreatine. Thus the creatine level of muscle indicates the phosphocreatine level with considerable accuracy and serves as an index to the energy available for muscular contraction. A loss of creatine is observed in the post-mortem examination of muscle of individuals who had wasting diseases. Myers,[2] Gross and Sandberg,[3] Herrmann and Dechard,[4] Linegar and associates[5] and others have found consistently a substantial decrease of the creatine content of both skeletal and cardiac muscle in human beings dead of cardiac failure. This occurs even in the presence of uremia with marked retention of other nitrogenous compounds. In living patients with heart failure no creatine levels of muscle have been reported. Beltrametti[6] in 1939 and, more recently, Sutton and Hinkens[7] have observed a marked elevation of the whole blood creatine levels of individuals with obviously failing hearts. Such observations are paralleled by those of Eppinger and associates,[8] Jeryell,[9] Meakins and Long[10] and others who found elevated lactic acid content in peripheral venous blood in cardiac insufficiency. Since lactic acid is a degredation product of creatine metabolism, these observations are pertinent to the study of blood creatine. Nylin[11] has speculated that the altered lactic acid level is related to the increased standard oxygen metabolism which is seen in persons with cardiac insufficiency. The role of the liver in creatine metabolism is unknown. It has been established that in myocardial infarction in both human beings and animals,

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the infarcted area loses creatine, and there is an associated creatinuria proportional to the size of the infarct.[4] Otherwise the relationship between the known loss of muscle creatine with infarction, with the presumed anoxia of cardiac failure and the concomitant increase of creatine in the blood has not been directly established. Post-mortem studies have indicated that both skeletal and cardiac muscle roughly parallel each other and lose creatine preterminally in cardiac failure. The authors have reported previously on creatine levels of biopsied muscle.[12] The possible effect of therapy on the muscle levels in man is also unknown. The apparent parallelism between skeletal and cardiac muscle creatine levels gives an indirect approach to the study of changes in myocardial energy, that is, myocardial phosphocreatine levels.

On the whole, studies of creatine in the blood have been confined to the serum. The Jaffé reaction with alkaline picrate gives not only the creatinine values (creatine determination depends on its breakdown to creatinine by hydrochloric acid) but also any other chromogens that will react with alkaline picrate. In blood serum this reaction for "apparent" creatine is thought to be 80 to 100 per cent specific (the serum contains less than 20 per cent chromogens other than creatinine).

There are, however, larger amounts of other chromogens in the red blood cells, so that only about 50 per cent of this total is thought to be creatine. This separation of true creatine content from the apparent level given by the Jaffé reaction with all chromogens is based on an enzymatic method which is technically difficult.

Studies involving whole blood creatine (Jaffé reaction) levels involve an appreciable amount of chromogens other than creatine from the red cells, and enzyme methods show that approximately 25 per cent of the whole blood creatine is in the serum and 75 per cent in the red blood cells. This fact has limited interest in this determination of whole blood creatine levels just as the technical difficulties of the enzymatic method have limited interest in it.

In our previous studies,[7] although elevations in whole blood creatine (Jaffé chromogen values) were found in many conditions, the greatest changes were noted in the blood of patients with cardiac decompensation. This is confirmatory of the earlier work of Beltrametti[6] who reported elevated whole blood and urine creatine levels in heart failure.

Creatine values given throughout this report are those obtained by the Jaffé method, realizing that some of the apparent creatine is composed of other chromogenic compounds. Most of the studies relating to our work are based on similar methods. The determination of the creatine content of muscle by the Jaffé method is highly accurate.[13]

The present report is intended to correlate these studies with further observations of the possible effects of various types of therapy on creatine levels.

PROCEDURE AND RESULTS

Whole blood creatine was determined by Folin and Wu's picric acid method as modified for the photolometer by Hoffman.[14] Blood samples were obtained from the anticubital vein without a tourniquet in place. Tissue creatine was determined by the method of Rose, Helmer, and Chanutin as modified for the photolometer.[14,15] Skeletal muscle creatine content was determined in duplicate, using one gram of muscle obtained by biopsy of the gastrocnemius muscle using local anesthesia of the skin.

I. *Experimental Error.*—Whole blood creatine was determined in sixteen duplicate samples from one individual. The experimental error in this laboratory was ±0.099 mg. per cent. Tissue creatine was determined on twenty one-gram pieces of gastrocnemius muscle from an individual dead four hours. These were analyzed in duplicate with an experimental error of ±16 mg. per cent with a mean of 416 mg. per cent.

II. *Whole Blood and Muscle Creatine Values in the Various Groups (Tables I and II).*—

TABLE I. COMPARISON OF MEAN WHOLE BLOOD CREATINE VALUES (MG.%) IN A GROUP OF NORMAL INDIVIDUALS, NONCARDIAC HOSPITAL PATIENTS, ANEMIC OR ANOXIC INDIVIDUALS, AND CARDIAC DECOMPENSATED PATIENTS

GROUP	NUMBER	MEAN CREATINE MG. %	GROUP MINIMUM MG. %	GROUP MAXIMUM MG. %	STANDARD DEVIATION	P VALUE
Normal	40	1.57	1.0	2.6	0.368	—
Noncardiac patients	118	2.18	1.0	4.5	0.73	0.1
Anemic and anoxic	17	3.91	3.1	4.9	0.551	0.01
Decomp. group	150	5.23	3.0	10.7	1.80	0.01

Values of P refer to the calculated probability of each group considered being included in the normal control group by chance and are based upon the calculation of "t" (Fisher, R. A., and Yates, F.: *Statistical Tables*, Edinburgh, 1938, Oliver and Boyd) for each group in comparison to the control group.

A. *Control group*: Creatine values of whole blood were determined in forty healthy adults, mostly men. Total blood creatine varied from a minimum of 1.0 mg. per cent to a maximum of 2.6 mg. per cent with a mean of 1.6 and standard deviation of ±0.368 mg. per cent (Table I).

Tissue creatine was not determined on normal biopsy material. Total creatine distribution in the blood as determined by triplicate examinations of fifteen samples revealed approximately 25 per cent in the serum and 75 per cent in the red blood cells.

B. *Hospital patient group*:

1. Total blood levels. A total of 118 individuals, mostly men, representing a cross section of a general medical ward in a charity hospital were studied. Individuals with anemia, diabetes, anoxia, azotemia or cardiac failure were excluded. This group of 118 patients with various diseases had a maximum value of 2.9 mg. per cent (minimum of 1.6 mg. per cent, with a mean of 2.2 mg. per cent, and standard deviation of ±0.73 mg. per cent (Table I).

2. Tissue creatine levels. Biopsied muscle specimens were studied in five men hospitalized with various diseases: two ambulant patients, one with a mild stroke and another with a healing duodenal ulcer had levels of 365 and 315 mg. per cent, respectively. One badly debilitated bedridden man with a cardiovascular accident had a muscle creatine value of 235 mg. per cent. Two other patients were studied: one case of carcinoma of the lung, 240 mg. per cent; and one with a severe cerebral vascular accident had a value of 255 mg. per cent. The mean whole blood creatine value was 4.8 mg. per cent (S.D. ± 1.6) and the mean muscle creatine level was 282.0 mg. per cent (S.D. ± 56.2).

C. *Effect of local anoxemia*: Blood creatine values were determined in sixteen individuals after application of a constrictor to the arm. Blood was withdrawn from the right arm for control and from the left after 20 minutes of continuous constriction sufficient to obstruct venous return. This resulted in an increase in every case and the increase of creatine varied from 0.9 to 6.7 mg. per cent with an average increase of 2.4 mg. per cent. No muscle creatine determinations were made on this group.

TABLE II. WHOLE BLOOD AND GASTROCNEMIUS MUSCLE CREATINE LEVELS IN NONCARDIAC DISEASE, IN CARDIAC PATIENTS BEFORE AND AFTER COMPENSATION, AND IN CARDIAC PATIENTS BEFORE AND AFTER COMPENSATION WITH ALPHA-TOCOPHEROL

GROUP	GROUP NO.	CONTROL LEVELS		COMPENSATED WITH DIGITALIS		COMPENSATED WITH DIGITALIS AND ALPHA-TOCOPHEROL	
		BLOOD (MG. %)	MUSCLE (MG. %)	BLOOD	MUSCLE	BLOOD	MUSCLE
Noncardiac disease	5	4.8	282.0	—	—	—	—
S.D. (σ)		1.6	56.2	—	—	—	—
$2\left(\frac{\sigma}{\sqrt{n}}\right)$		1.43	50.1	—	—	—	—
		Decompensated Status					
Cardiac patients							
S.D. (σ)	18	6.17	255.5 (M_1)	3.36	329.8 (M_2)	—	—
$2\left(\frac{\sigma}{\sqrt{n}}\right)$		1.6	48.8	0.8	38.6	—	—
		0.75	23.02	0.51	24.1	—	—
2 E (M_1-M_2)		—	29.8	—	—	—	—
2 E (M_2-M_4)		—	—	—	31.2	—	—
Cardiac patients							
S.D. (σ)	10	6.21	245.3 (M_3)	—	—	3.4	412.0 (M_4)
$2\left(\frac{\sigma}{\sqrt{n}}\right)$		0.8	26.8	—	—	0.41	39.3
		0.51	16.9	—	—	0.27	26.2
2 E (M_3-M_4)		—	30.0	—	—	—	—

D. *Group of patients with anemia or systemic anoxia*: The blood of seventeen individuals having varying degrees of cyanosis and anemia was analyzed. Pneumonia was the cause of cyanosis while those patients with acute anemias had bleeding gastric or duodenal ulcers. The maximum value was 4.9 mg. per cent, minimum 3.1 mg. per cent, with a mean of 3.91 mg. per cent and a standard deviation of ± 0.551 mg. per cent (Table I).

E. *Group with cardiac decompensation*: A selected group of 150 cases of heart failure (Grade 4, American Heart Association) was studied prior to therapy. The usual criteria for this diagnosis were used, e.g., cardiac enlargement, changes in rhythm, dyspnea, cyanosis, and edema. The maximum value was 10.7 mg. per cent, minimum 3.0 mg. per cent, with a mean of 5.23 mg. per cent, and a standard deviation of ±1.8 mg. per cent (Table I).

TABLE III. SELECTED CASES FROM A GROUP OF 25 PATIENTS WITH FOLLOW-UP DETERMINATIONS

CASE	DIAG.	AGE	DATE	PERI-PHERAL EDEMA	HEPATO-MEGALY	DYSPNEA	PULM. EDEMA	CREATINE
1	ASHD	52	12/27/49	4	4 F	Severe	3	10.5
			12/28/49	2	2 F	Moderate	1	5.4
			12/29/49	0	2 F	Slight	0	3.0
4	Hypert.	65	1/ 4/50	2	0	Severe	4	4.2
			1/ 5/50	0	0	Slight	0	1.1
6	RHD	45	3/ 6/50	4	5 F	Severe	3	6.0
			3/ 8/50	0	3 F	Slight	0	1.4
8	ASHD	64	3/16/50	4	5 F	Severe	4	6.4
			3/17/50	1	3 F	Moderate	2	4.3
			3/19/50	0	3 F	Moderate	0	2.2
9	ASHD	63	3/28/50	4	2 F	Slight	1	4.4
			3/29/50	0	2 F	Slight	0	2.3
			4/ 1/50	0	0	0	0	1.9
10	RHD	45	3/16/50	4	6 F	Severe	3	6.5
			3/17/50	2	4 F	Moderate	2	2.7
12	ASHD	62	4/18/50	4	2 F	Moderate	2	4.9
			4/19/50	1	2 F	Slight	1	2.6
13	Hypert.	69	1/18/50	0	0	0	0	2.9
			1/19/50	0	0	Moderate	0	4.3
			1/21/50	4	—	Severe	3	7.3
15	ASHD	78	3/31/50	3	3 F	Moderate	2	4.2
			4/ 2/50	3	3 F	Moderate	2	5.6
			4/ 4/50	4	4 F	Severe	4	6.4
18	ASHD	66	4/27/50	4	3 F	Moderate	1	4.7
			4/28/50	3	2 F	Slight	0	2.7
19	RHD	62	6/23/50	4	5 F	Moderate	3	4.6
			6/24/50	2	3 F	Moderate	1	3.5
			6/25/50	1	3 F	Slight	0	2.8
21	RHD	42	4/21/50	4	—	Severe	3	4.9
			4/22/50	1	—	Moderate	1	3.2
			4/23/50	0	—	Moderate	0	2.8

ASHD = Arteriosclerotic heart disease; Hypert. = hypertensive heart disease; RHD = rheumatic heart disease.

F. *Group of individuals with cardiac decompensation studied with repeated determinations:* A group of twenty-five individuals were studied with a determination of whole blood creatine at the time of admission and at approximately 24-hour intervals thereafter until clinical improvement or death occurred. Analysis of this group shows that creatine blood values varied directly with the degree of failure. As an example, a man with persistent cyanosis due to silicosis entered the hospital on March 16 in severe failure. The blood creatine then was 8.3 mg. per cent. On the third day the condition was improved and the creatine was down to 4.0 mg. per cent. On the seventh day the clinical condition became worse and the creatine was 6.8 mg. per cent. He left the hospital but returned on June 27 with moderate failure and a creatine of 5.5 mg. per cent. By the fifth day marked improvement was evident and the creatine was 3.3 mg. per cent. In this instance, the variations in blood creatine fluctuated with degree of cardiac compensation, although there was continuous severe cyanosis. In twenty-one cases who improved clinically, the blood creatine fell rapidly to levels comparable with the normal or hospital groups, namely, a mean of 3.36 mg. per cent (selected cases presented in Table III). Those cases which continued in chronic failure or went on to death maintained high or increasing levels, respectively (Table IV).

TABLE IV. SERIAL CREATINE VALUES IN PATIENTS DYING OF HEART FAILURE

CASE	DIAG.	AGE	DATE	PERIPHERAL EDEMA	HEPATOMEGALY	DYSPNEA	PULM. EDEMA	CREATINE
22	ASHD	72	4/24/50	4	—	Severe	4	5.4
			4/25/50	2	—	Moderate	2	4.1
	Death		4/26/50	1	0	Severe	4	7.7
23	RHD	59	1/10/50	1	0	Slight	0	2.6
			1/15/50	2	2 F	Moderate	1	3.4
			1/18/50	4	2 F	Moderate	2	4.9
	Death		1/19/50	Anasarca	?	Severe	4	7.1
24	RHD	30	1/18/50	Anasarca	—	Severe	4	8.8
	Death		1/19/50	Anasarca	—	Severe	4	13.2
25	ASHD	60	2/16/50	0	0	Slight	0	1.5
			2/27/50	3	3	Moderate	2	5.6
	Death		3/12/50	4	3	Severe	2	4.6

See Table III for legend.

Tissue creatine was studied in biopsy material from twenty-eight of these decompensated patients prior to therapy. This group had a minimum of 195 mg. per cent, maximum of 395 mg. per cent, and a mean of 251. Blood creatine values taken at the time of biopsy averaged 6.2 mg. per cent. In ten of these patients a second muscle biopsy was done 10 to 14 days later when the patients were clinically compensated after the usual therapeutic procedures (digitalis, barbital, diuretics). The tissue creatine rose in all cases to a mean value of 329.8 mg. per cent, while the whole blood level had dropped to a mean value of 3.4 mg. per cent.

A similar study was made of total blood creatine and tissue creatine before and after compensation in ten patients who were given alpha-tocopherol (50 mg. daily) in addition to cardiac therapy identical to the previous group not given alpha-tocopherol. Initially, the skeletal muscle had a mean creatine value of 245.3 mg. per cent, and the blood level was 6.2. Ten to fourteen days later after clinical evidence of compensation the tissue creatine value was 412 mg. per cent, and the whole blood level was 3.4. This is a significant rise in muscle creatine level over the mean of 329.8 mg. per cent found in those compensated without alpha-tocopherol (Table II).

All data was subjected to statistical analysis following the procedures of Fisher[16] and the results presented in the appropriate tables. The standard deviation was $(\sigma) = \sqrt{\frac{\sum x^2}{(n-1)}}$, and the standard error of the mean $(S_{\bar{x}}) = \frac{\sigma}{\sqrt{n}}$. The standard error of the difference between two means was calculated by the formula S.E. $E = \sqrt{\frac{\sigma^2}{n} + \frac{\sigma_1^2}{n_1}}$. Differences between two means exceeding thrice this figure were considered highly significant.* The value of "t" was obtained from the formula $\pm t = \frac{(\bar{x} - m)}{S_{\bar{x}}}$ and the value of P obtained from the charts of Fisher and Yates.[17] If P was 0.01 or less, it was unlikely that the study group was included in the control group.

DISCUSSION

1. Allison,[18] using the enzyme method, found a "true creatine" level in the red blood cells to be 2.88 and 3.26 mg. per cent in two normal persons and 0.2 and 0.6 mg. per cent in the serum. Beard,[19] using the Jaffé reaction, obtained values of about 3 mg. per cent in whole blood.

The results of the present larger series of determinations of the creatine level of normal persons by the Jaffé reaction (i.e., the total chromogen) indicate that the mean level of creatine may be slightly lower. The error introduced by the use of the Jaffé method at such levels appears to be minimal.

2. Blood creatine levels in men with various diseases, excluding those with azotemia, anemia, anoxia, diabetes or cardiac failure are reported. This level of 2.18 mg. per cent is higher than that of the normal group but is a statistically insignificant change.

3. Since this report is the first on muscle creatine levels obtained by biopsy, the levels obtained can be compared only to those found in cadavers. The mean skeletal muscle creatine of twenty-eight patients in cardiac failure was 251 mg. per cent, and this value for five patients with noncardiac disease was 282 mg. per cent. These levels are very low and are essentially in agreement with the observations on post-mortem muscle specimens made by Corsaro and associates,[20] who found low values in many diseases.

*Note: The authors wish to emphasize that the levels of the various groups considered as "significantly different" in this report exceeded necessary statistical criteria by several times. Most of the differences between means exceeded by five to six times the standard error of the differences between them.

4. The role of anoxemia and heart failure in changing muscle metabolism with increase in creatinuria has been emphasized by Herrmann.[4] The rapid rise in total blood creatine observed in the present experiment with localized venous obstruction and resultant anoxia of muscle groups of normal persons indicates that anoxia is an important factor.

5. Total blood creatine was significantly elevated in anemia and in cyanosis associated with pneumonia. Both of these conditions have the common factor of generalized tissue anoxia without wasting. The elevated whole blood creatine levels observed in living human beings in this series is paralleled by the observation that the skeletal muscle of those individuals whose death was caused by these conditions had lowered creatine levels.

6. Beltrametti[6] has previously reported elevated whole blood creatine in cardiac failure. Cardiac failure caused a much greater increase in blood creatine than was observed in a control group of individuals with sundry diseases, with anemia, or with anoxia. Also, there was an obvious and striking relation between the degree of failure and blood creatine level for any individual. There was no apparent relation between the absolute height of the initial creatine level and the course or eventual outcome. However, all individuals in failure had a higher than normal initial level, and this level fell rapidly (within 24 to 48 hours) with compensation. With advancing failure and death the levels remained high or increased.

7. Cardiac failure also caused a marked drop in skeletal muscle creatine. The only reported values of muscle creatine are from autopsy material which indicate a normal level of about 400 mg. per cent.[5,20]

In the present series of patients in congestive failure the level was 251 mg. per cent. The tissue creatine rose in all cases to 329.8 mg. per cent with compensation. This level of 329.8 mg. per cent, however, was still subnormal. These lower levels for clinically compensated patients may be significant as muscular fatigue is a common complaint of patients with subclinical failure.

These observations on living tissue confirm previous findings at autopsy of individuals dead of heart disease, i.e., all have lowered skeletal muscle creatine during decompensation.[3,5] With compensation the skeletal muscle creatine was rapidly restored.

Since it is known that persons whose deaths were caused by heart disease have lowered creatine levels in heart and skeletal muscle it may be surmised that parallel changes occur in the living heart muscle, that is, creatine decrease with cardiac failure and creatine increase with compensation.

8. Evidence in experimental animals indicates that alpha-tocopherol causes a 20 to 36 per cent increase in skeletal muscle creatine.[19] In this study the administration of this substance during the period of cardiac compensation caused no change in total blood creatine levels, different from control groups. With alpha-tocopherol administration, skeletal muscle creatine levels, identical to the control group at the time of admission in failure, were raised well above the control group by the time the patient was compensated. The mean for this group (412.0 mg. per cent), all of whom were cardiac patients in a temporarily compensated state, was, nevertheless, well within the range of normal reported from autopsy.

This level (412.0 mg. per cent) is 82.2 mg. per cent greater than the mean muscle creatine level (329.8 mg. per cent) of those patients compensated without alpha-tocopherol. There was no apparent clinical effect of alpha-tocopherol.

CONCLUSIONS

The results of these experiments indicate:

1. Local and systemic anoxia, in the absence of other factors such as wasting or starvation, caused significant elevation of blood creatine.

2. Cardiac failure caused the greatest elevation of whole blood creatine, and compensation lowered this level toward normal. The change in any individual usually preceded clinical change and would fall with clinical improvement, rise with worsening status. Whole blood creatine levels may thus serve as prognostic aids.

3. Cardiac failure was associated with a marked decrease in skeletal muscle creatine, and this rose toward normal levels with improvement in cardiac status. This low level may be intimately connected with the muscular fatigue of cardiac failure.

4. Alpha-tocopherol given during therapy for cardiac failure caused a greater increase in skeletal muscle creatine to normal levels. There was no apparent clinical effect.

SUMMARY

1. Values for the creatine content of whole blood have been determined for: (a) normal individuals, (b) patients suffering from various illnesses, (c) those with cyanosis or anemia, and (d) cases of cardiac failure before and after compensation.

2. The elevation of creatine values in heart failure bore a relation to the degree of decompensation. Decreasing values indicated improvement, while stationary, high, or increasing values indicated severe cardiac failure, often impending death. On this basis serial levels may be of prognostic value.

3. Fatigue, an important early symptom of impending cardiac decompensation, may be due to a decrease of elements essential to muscle contraction, of which creatine is one.

The values of biopsied muscle creatine showed a similar but opposite variation to those observed in blood, i.e., cardiac failure is accompanied by increase of creatine in the blood and decrease in the muscle. With return of compensation, this relationship is reversed.

Vitamin E caused an increase of muscle creatine above that resulting from compensation only.

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CERTAIN CARDIOVASCULAR EFFECTS OF VASOPRESSIN (PITRESSIN)

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CERTAIN untoward effects that have been considered to be cardiac in nature have resulted occasionally from the use of vasopressin (Pitressin). These adverse consequences prompted study of the cardiovascular effects of this drug when it was administered intravenously all at once or during a period of thirty minutes.

SURVEY OF THE LITERATURE

Resnik and Geiling[1] reported that pituitary extract affects the heart by stimulation of the vagi through the cardio-inhibitory center and by direct action on the myocardium. They noted similarities between the effects on the heart of pituitary extract and anoxemia.

Grollman and Geiling[2] found that extract of the posterior lobe of the pituitary body (Pituitrin) and Pitressin produce for a brief period decreases in pulse rate, consumption of oxygen and cardiac output; these decreases were succeeded by prolonged increases in these functions. These subsequent increases in cardiac output and pulse rate were attributed to the accumulation of catabolites during the period of decreased consumption of oxygen after administration of Pituitrin and Pitressin.

Geiling and DeLawder[3] found that after injection of Pitressin a state developed that resembled anaerobic metabolism in the tissues drained by the superficial and deep veins of the legs of dogs. During this time the color and the content of oxygen of venous blood resembled those of arterial blood. This was a period of decreased cardiac output and lowered basal metabolic rate. They also noted an extensive decrease in the consumption of oxygen during the period of maximal action of Pitressin, which was followed by a more prolonged period during which consumption of oxygen was greater than the initial value; after this a gradual return to normal took place (Geiling and DeLawder).[4]

Geiling[5] stated that therapeutic doses of Pitressin given intramuscularly or subcutaneously did not cause any significant increase in blood pressure in spite of the associated great pallor which might lead to the inference of increase in arterial tension. A decided but brief decrease occurred in pulse rate, consumption of oxygen and cardiac output, which was followed by a more prolonged increase. In trained dogs, larger doses given intravenously had an effect that was more intense but that was essentially similar to the effect found in man except for the change in blood pressure. For a brief period, the character of venous blood approached that of arterial blood, owing to failure of the body to take up oxygen. During this time, the consumption of oxygen decreased greatly and a reduction in blood flow took place. Small doses given to anesthetized dogs or cats caused a sharp increase in blood pressure as the result of peripheral vasoconstriction. Larger doses caused a decrease in blood pressure, followed by an increase. Geiling suggested that the decrease in blood pressure was caused by constriction of coronary vessels; the depressor action was cardiac and the tolerance factor was vested in peripheral structures.

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Katz and Lindner[6] observed that Pitressin caused powerful constriction of the coronary vessels that continued for a half hour or more without appreciably lessening in degree. Gruber and Kountz[7] concluded that in the nonanesthetized dog Pitressin affects the heart by (1) reflex stimulation of the vagi through the cardio-inhibitory center, (2) direct action on cardiac muscle, and (3) coronary vasoconstriction, with production of a deficient supply of blood to the myocardium.

Holtz[8] reported that pituitary extracts had no action on pulmonary vessels. Administration of Pitressin increased pressure in the pulmonary arteries of cats; this was secondary to an increase in coronary flow. Pituitary extracts decreased the pulmonary arterial pressure in rabbits and dogs because of diminution in coronary flow. Pituitary extracts caused decreased pressure in the portal veins of dogs and cats.

Ruskin[9] found that Pitressin brought about coronary spasm and relative myocardial ischemia, either of which may cause anginal pain.

According to Burstein,[10] the detrimental effects observed after administration of Pitressin were (1) decrease in arterial pressure after a preliminary temporary increase, (2) constriction of coronary vessels, (3) cardiac irregularities, (4) increased secretion of mucus and laryngospasm during anesthesia, and (5) bronchospasm, especially in patients who had asthma. Graybiel and Glendy[11] noted an average decrease of 5 per cent in cardiac output in six persons after administration of Pitressin. With the amount used, no evidence was present of significant cardiovascular symptoms in either normal persons or patients who had cardiac disease. The authors suggested that Pitressin may be injected slowly intravenously in amounts sufficient to produce extensive gastrointestinal symptoms without the production of alarming or even significant circulatory symptoms. They concluded that Pitressin may be given in therapeutic amounts without fear of untoward cardiovascular effects.

Dearing and associates[12] observed myocardial lesions that were most prominent in the subendocardial layer of the left ventricular musculature after repeated administration of large doses of Pitressin. Woodbury and Ahlquist[13] reported transient increase in cutaneous blood flow and decrease in flow through the vessels of muscular regions after intravenous injection of Pitressin. They found no evidence for direct inhibition of oxidative processes by Pitressin but noted that, by means of vasoconstriction, Pitressin restricts the amount of oxygen available in tissues and thereby limits oxidative processes.

Because Pitressin was found to be a powerful constrictor of coronary vessels (Katz and associates)[14] and might be expected to act detrimentally on the healing of infarcts, Mintz and Kondo[15] gave it subcutaneously to dogs whose left descending coronary arteries had been ligated. The drug was given in doses of 20 pressor units daily for two weeks and then six times weekly for four weeks. Necropsy was done after this course of treatment; the ligation of the coronary artery in each dog was checked, and the endocardial aspect of the infarct was traced carefully. Pitressin given in this fashion failed to affect the size of the infarct produced by such experimental ligation.

Essex and his associates[16] and Wégria, working with the same group,[17] reported that the mean inflow of the coronary arteries was reduced by intravenous injection of Pitressin into anesthetized as well as nonanesthetized dogs despite the increased blood pressure. Green and co-workers[18] reported that intracoronary injection of Pitressin caused intense constriction of the coronary vessels and reduction of coronary flow sufficient to depress the contractile effort of the myocardium.

METHODS

The present study was made on dogs which received Pitressin intravenously in doses of 0.1 to 1 unit per kilogram of body weight either at once or by infusion during a period of thirty minutes. In one portion of the study the animals were anesthetized with pentobarbital sodium and were given 100 per cent oxygen by means of a closed-circuit spirometer throughout the period of observation. The cardiac rate was recorded electrocardiographically and by means of a cardiotachometer. Cardiac output was determined by application of the Fick principle,

using measurements of oxygen content of arterial and mixed venous blood, and of the oxygen consumed by the animals. Systolic and diastolic blood pressures were recorded galvanometrically on photosensitive paper by means of strain gauges connected to cardiac catheters.

Guided by roentgenoscopic examination, a single-lumen cardiac catheter was passed through the exposed carotid artery and through the left ventricle and left atrium until the tip of the catheter was located in either the left atrium or one of the main pulmonary veins. A double-lumen cardiac catheter was introduced through the jugular vein and through the right atrium and right ventricle into the pulmonary artery until its tip was wedged in one of the small branches of the pulmonary artery; the proximal orifice, 6 cm. back of the tip, thus was located in the pulmonary artery. Another strain gauge recorded the systemic blood pressure through an internally polished 20-gauge needle that was inserted into the lumen of the femoral artery in the femoral triangle.

In another part of this study, the blood flow was repeatedly measured in anesthetized heparinized dogs from one or both femoral arteries by use of bubble flowmeters.

In order to determine the effects of Pitressin on the oxygen in the blood, samples of blood from the femoral artery and femoral vein were taken from a number of dogs before and within two minutes after intravenous injection of Pitressin and at specified intervals thereafter for twenty minutes. All samples of blood were analyzed by the Van Slyke procedures for oxygen content, capacity, and saturation.

RESULTS

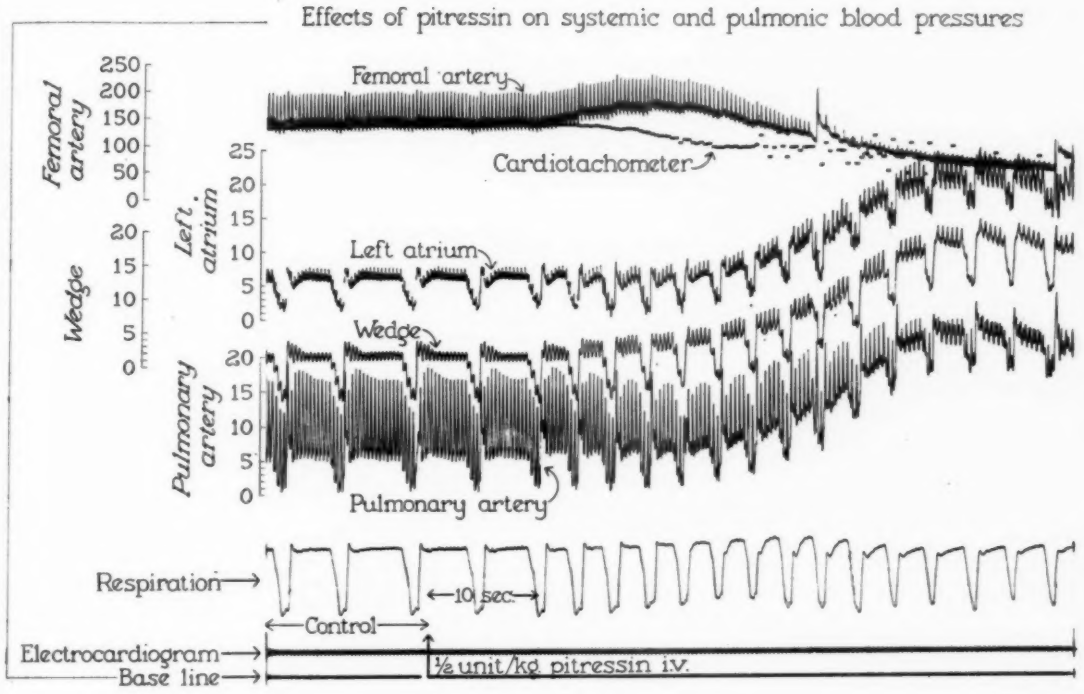
Immediately after intravenous injection of Pitressin in doses of 0.1 to 1 unit per kilogram of body weight, a primary increase in both systolic and diastolic femoral arterial pressures occurred, accompanied by slight reduction in cardiac rate and increase in respiratory rate. These changes were soon succeeded by increases in systolic and diastolic pressures in the left atrium, in wedge pressure and in pulmonary arterial pressure, all of which usually reached a peak coincident with a secondary decrease in the femoral arterial pressure. These changes in pressure were accompanied by great reduction in pulse pressures. Figure 1 shows two representative examples of continuous records of the responses to intravenous administration of Pitressin. When only 0.1 unit of Pitressin per kilogram of body weight was given intravenously, the changes in the various parts of the pulmonic and systemic vascular systems were in the same direction as those seen when the dose was increased to 0.5 unit, but the magnitude of change was smaller. Irregularities in cardiac rhythm often occurred at the peak of the effects of Pitressin and sometimes lasted throughout the period of observation.

Great reduction in cardiac output, as determined by the Fick principle during three successive ten-minute intervals, was present after intravenous administration of Pitressin. Table I shows a reduction of 24 to 71 per cent from the control values in the cardiac output of ten animals after administration of Pitressin. The use of this drug also produced a delayed but definite reduction in venous content of oxygen.

TABLE I. EFFECTS OF INTRAVENOUS ADMINISTRATION OF PITRESSIN

DOG	DOSE, UNIT PER KILOGRAM	CONDITION*	TOTAL O_2 CONSUMPTION, C.C. PER MIN.	OXYGEN CONTENT OF BLOOD, C.C. PER 100 C.C.		CARDIAC OUTPUT		CARDIAC RATE, BEATS PER MIN.	
				VENOUS	ARTERIAL	LITERS PER MIN.	REDUCTION (%)	TOTAL	REDUCTION
1	1	Control	91.8	16.0	20.2	2.185		154	
		1	77.5	10.9	19.9	0.860	−61	132	−22
		2	80.1	11.9	19.4	1.068	−51	146	−8
		3	90.7	13.0	20.1	1.277	−42	145	−9
2	1	Control	102.5	13.4	15.3	5.394		156	
		1	82.0	10.8	15.7	1.673	−69	89	−67
		2	86.4	11.2	16.6	1.600	−70	88	−68
		3	97.3	10.8	16.5	1.707	−68	92	−64
3	1	Control	157.0	14.4	17.7	4.758		170	
		1	86.4	12.3	17.4	1.694	−65	146	−24
		2	86.4	11.9	17.1	1.661	−65	157	−13
		3	97.4	10.7	16.2	1.771	−63	155	−15
4	1	Control	170.0	18.5	22.0	4.857		155	
		1	106.0	14.2	20.8	1.606	−67	148	−7
		2	84.5	15.0	20.8	1.457	−70	148	−7
		3	81.0	15.2	20.9	1.421	−71	148	−7
5	1	Control	100.0	13.5	18.4	2.041		126	
		1	89.0	11.4	18.0	1.348	−34	117	−9
		2	84.8	11.9	17.7	1.462	−28	122	−4
		3	93.4	11.3	17.3	1.557	−24	125	−1
6	1	Control	113.7	19.1	21.8	4.211		161	
		1	75.7	15.8	21.7	1.283	−69	100	−61
		2	103.2	15.3	21.4	1.692	−59	107	−54
		3	150.8	15.3	21.4	2.472	−41	126	−35
7	0.5	Control	82.0	15.2	19.5	1.644		188	
		1	47.9	11.2	18.6	0.647	−60	154	−34
8	0.5	Control	125.2	18.3	20.9	4.815		135	
		1	66.9	17.7	20.0	2.909	−39	113	−22
9	0.5	Control	119.7	14.6	19.9	2.258		186	
		1	80.2	14.4	20.1	1.407	−37	151	−35
10	0.1	Control	71.7	15.9	20.3	1.414		202	
		1	46.1	16.4	21.3	0.817	−41	154	−48

*1 = first ten minutes; 2 = second ten minutes; 3 = third ten minutes.



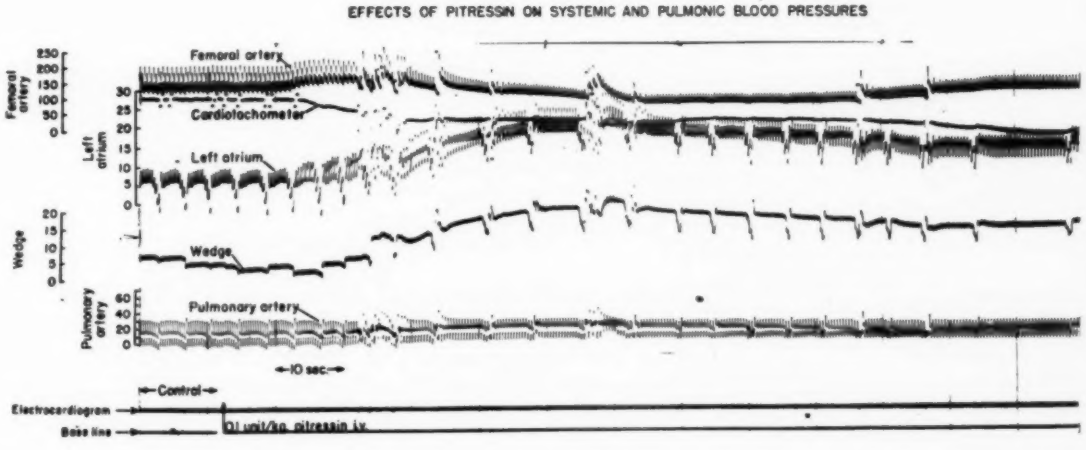


Fig. 1.—Two tracings showing effects of administration of Pitressin on cardiac and respiratory rates and on systolic and diastolic pressures in the systemic and pulmonic circulation.

*1 = first ten minutes; 2 = second ten minutes; 3 = third ten minutes.

Extensive reduction in blood flow was noted in the femoral vessels; this lasted for about two hours. Figure 2 presents records obtained from three dogs in which the blood flow in the femoral artery was measured before, during, and for twenty minutes after administration of Pitressin in a dose of 1 unit per kilogram of body weight. Occasionally a slight transient increase in blood flow occurred initially, as noted in dogs 1 and 2.

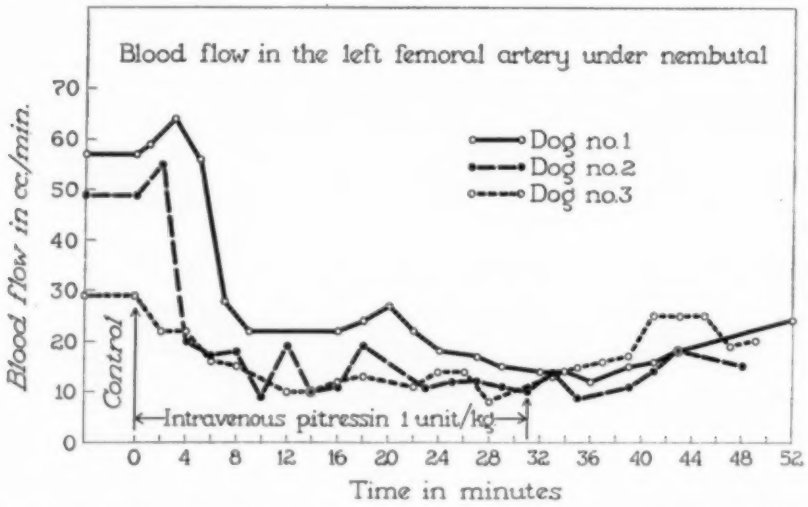


Fig. 2.—Curves of blood flow before, during, and after intravenous administration of Pitressin.

COMMENT

Administration of Pitressin caused definite reduction in pulse pressure, which was observed especially in tracings of the femoral arterial blood pressure. Furthermore, it caused great reduction in cardiac output for at least thirty minutes and extensive reduction in blood flow in the femoral artery (Fig. 2) similar to that reported for the coronary artery. All these findings may be taken to indicate that use of Pitressin produces ischemia of the myocardium, the duration of which depends on the dosage and the route of administration. One of the dogs in this study died within three minutes of the administration of Pitressin. Necropsy revealed old infarcts and a fibrotic myocardium. No other acute or chronic lesions or damage could be found in the other organs of this animal; death was attributed to myocardial ischemia produced by Pitressin in a heart that was the seat of previous infarction and fibrosis. These findings justify a word of caution in the use of Pitressin, especially in patients who present any history of myocardial damage.

SUMMARY

Pitressin was administered intravenously in doses of 0.1 to 1 unit per kilogram of body weight either at once or during a period of thirty minutes to dogs which were anesthetized with pentobarbital sodium. Cardiac output was determined by application of the Fick principle. Systolic and diastolic blood pressures at various points in the heart or pulmonary vessels were recorded by means of

strain gauges connected to cardiac catheters. Another strain gauge recorded the blood pressure from a needle inserted into the femoral artery. The blood flow was recorded in heparinized animals from one or both femoral arteries by use of bubble flowmeters.

Administration of Pitressin produced definite reduction in cardiac rate, consumption of oxygen, venous content of oxygen and cardiac output. Sometimes the heart became arrhythmic, and extrasystoles appeared soon after injection of Pitressin. Initially, transient increases were noted in both systolic and diastolic blood pressures in the femoral artery. This was soon followed by increases in the systolic and diastolic pressures in the pulmonary artery, in the wedge pressure in the small pulmonary vessels, and in pressures in the left atrium, while pressures in the femoral artery decreased to less than control values and the pulse pressure was much reduced. Administration of Pitressin produced great reduction in femoral blood flow.

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ANALEPTIC EFFECTS OF ARANTHOL IN VASOMOTOR DEPRESSION INDUCED BY QUINIDINE

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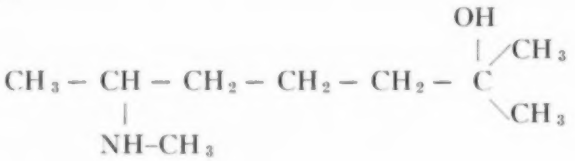
In previous comparative studies of Aranthol (EA–83, 2-methylamino-6-hydroxy-6-methylheptane), a synthetic aliphatic amine with the following structural formula



it was concluded that the action of this analeptic was chiefly on the cardiovascular system. Jackson[1] stated that in moderate dosages it had practically no effect on the central nervous system but that it was a strong cardiac stimulant and produced an "extensive and long-lasting" rise in blood pressure. Walton and Brodie[2] observed that it produced a consistent increase in isometric systolic tension and a moderate rise in blood pressure.

More recently, Boniface and Brown,[3] in experimental studies in dogs, evaluated three cardiovascular stimulant drugs—ouabain, ephedrine and Aranthol—in barbiturate cardiac depression. After infusion of pentobarbital sodium, they found that the cardiac arrest dose could be increased by only 50 per cent with ouabain but by about 200 per cent with either Aranthol or ephedrine. Ephedrine and Aranthol were about equal in their ability to antagonize the cardiovascular depression resulting from the infusion of massive doses of pentobarbital, but they considered Aranthol the preferable drug since ephedrine produced tachyphylaxis more readily.

In the present study, it is our purpose to (1) re-evaluate the analeptic value of Aranthol in normal dogs; (2) appraise its analeptic properties after administration of large doses of quinidine; and (3) compare the analeptic effects in combination with other drugs.

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METHODS AND MATERIALS

Experiments were conducted on thirty-eight dogs of varying weight, anesthetized with thiopental sodium. All drugs were administered intravenously, and the doses measured in milligrams per kilogram of body weight. Changes in pulse pressure were recorded as plus-minus, indicating little increase in stroke volume, or force of the contraction; two plus, indicating double volume; three plus, indicating trebled volume, etc. Respiratory changes in rate and amplitude were noted, and blood pressure was carefully recorded before and after administration of each drug. In the earlier experiments carotid artery blood pressures were recorded by means of a mercury manometer; later, a rubber diaphragm Hürthle manometer was used.

RESULTS

Aranthol Alone.—

Experiments were carried out in eleven dogs, to determine the effects of Aranthol (10 per cent; each cubic centimeter contains 100 mg.) alone in the normal anesthetized animal (Table I). In the doses used, Aranthol proved to be a powerful cardiovascular stimulant, causing rises in blood pressure of 100 per cent or more (Fig. 1*A*). In one dog, which received 13 mg. of Aranthol per kilogram of body weight (not included in the table), the blood pressure rose so high that all the mercury in the manometer was forced out. Usually about thirty minutes elapsed before the blood pressure returned to the preinjection level. A very short period of tachycardia was followed by a slowing of the cardiac rate. The over-all effect on respiration was not significant.

TABLE I. EFFECT OF ARANTHOL ON BLOOD PRESSURE, PULSE PRESSURE, AND RESPIRATION IN NORMAL DOGS

DOG NO.	WEIGHT KG.	ARANTHOL TOTAL MG.	DOSAGE MG./KG.	BLOOD PRESSURE (MM. HG)		PULSE PRESSURE*	RESPIRATION
				BEFORE ARAN.	AFTER ARAN.		
1	5.9	75	12.7	120	240	±	Slight increased rate and amplitude
2	11.3	100	8.9	120	240	3+	No effect
3	11.3	100	8.9	120	300	2+	No effect
4	12.7	100	7.9	120	180	2+	No effect
5	20.4	100	4.9	120	240	4+	Slight increased rate
6	20.4	75	3.7	120	132	3+	No effect
7	11.3	75	6.7	120	168	2+	Slight increased rate and depth
8	12.2	75	6.0	160	320	2+	No effect
9	7.7	50	6.5	135	168	4+	Slight increased rate
10†	11.4	11	1.0‡	120	130	2+	No effect
		22	2.0‡	120	140	3+	Slight increased rate
		44	4.0‡	120	182	4+	No effect
		55	5.0‡	124	190	4+	No effect
		77	7.0‡	130	205	4+	No effect

*Plus-minus (±) indicates slight increase in pulse pressure; 2+ indicates the pressure was doubled, 3+ trebled, etc.

†Five experiments on Dog 10.

‡Approximate.

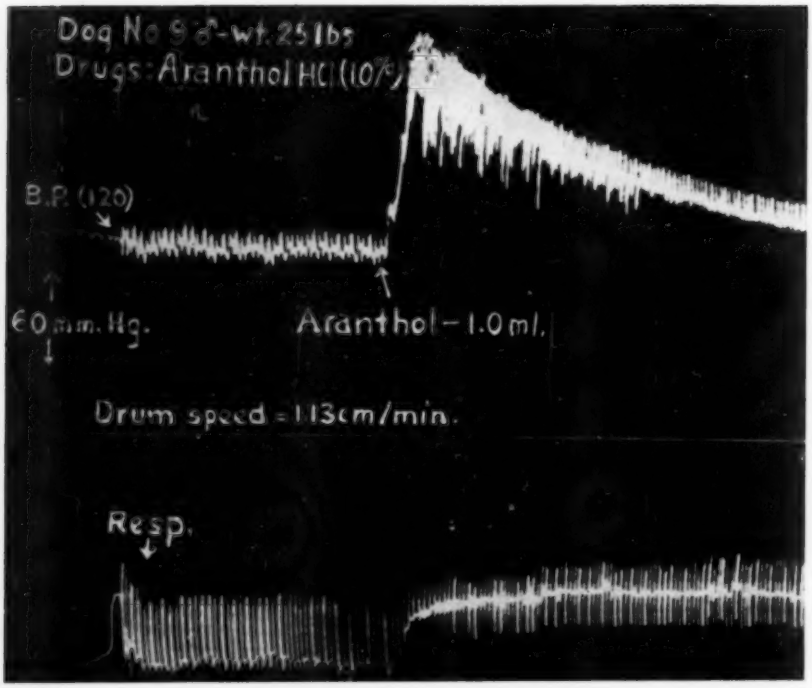

Fig. 1A.—Dog No. 9, male, weight, 25 lbs.; drugs: Aranthol HCl (10 per cent).

Fig. 1B.—Exper. No. 9. Dog No. 9. Aranthol, 1.0 ml.; Metrazol, 2.3 ml.

Relation of dose to action: Aranthol was given in doses of 1 to 50 mg./kg. to determine the optimum pharmacologic dose. The optimum effect was obtained with doses of 4 to 10 mg./kg. of body weight, which is in agreement with the results previously reported by Jackson. The blood pressure rises were directly proportional until a dose of about 10 mg./kg. was reached; doses exceeding this amount caused no further rise. The effect of varying doses of the drug was demonstrated in a male dog weighing 11.4 kilograms (Fig. 2). This was one of many experiments in which a Hürthle tambour manometer, for pulse pressure readings, and a mercury manometer, for blood pressure readings, were so arranged that we could readily switch from one to the other. The dog was allowed to

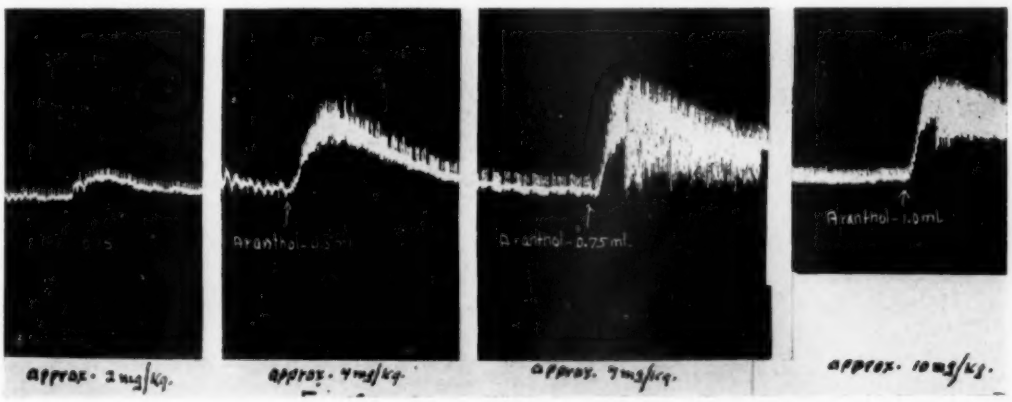

Fig. 2.—Dog, weight, 11.4 kg.

recover from one dose before the next dose was given. One mg./kg. caused a 100 per cent rise in pulse pressure; the blood pressure did not rise more than 10 mm. Hg, and no change was noted in respiration. Two mg./kg. effected a rise in pulse pressure of more than 100 per cent; the blood pressure increased to 140 mm. Hg, and the respiratory rate increased slightly. Four mg./kg. caused a rise in pulse pressure of almost 150 per cent; the blood pressure rose to 182 mm. Hg, but there was no change in respiration. Five mg./kg. caused a rise in pulse pressure of about 300 per cent; the blood pressure rose to 190 mm. Hg. Seven mg./kg. effected a 600 per cent increase in pulse pressure; the blood pressure rose to 205 mm. Hg. Doses larger than 7 mg./kg. failed to increase the pulse or blood pressures. In dogs rendered hypotensive by bleeding, Huggins and associates[14] showed that the intravenous administration of Aranthol in doses of 10 mg./kg. increased the cardiac output about 20 per cent. (We may assume, from the work of Walton and Brodie, that increased pulse pressure may be indicative of increased cardiac stroke volume.)

Electrocardiographic findings: With pharmacologic doses, the following electrocardiographic observations were made (Fig. 3): (1) the amplitude of the T wave was increased; (2) the Q-T interval was slightly increased; (3) extrasystoles were the first manifestations of toxicity; more pronounced irregularities followed as toxicity increased.

Toxicity: Doses of Aranthol in excess of 10 mg. produced definite evidence of toxicity, manifested first by the appearance of extrasystoles. A more pronounced toxic effect was noted on respiration, the first indication of which was a bigeminal type of breathing. Marked irregularities in heart action were noted with large dosages, and the thorax appeared to become contracted. The appearance of the chest indicated that there was a diminished amount of supplemental as well as tidal air. Excessive salivation and frothing from the mouth, which were also noted in experiments by Jackson[1] and by Walton and Belkin,[4] soon followed.

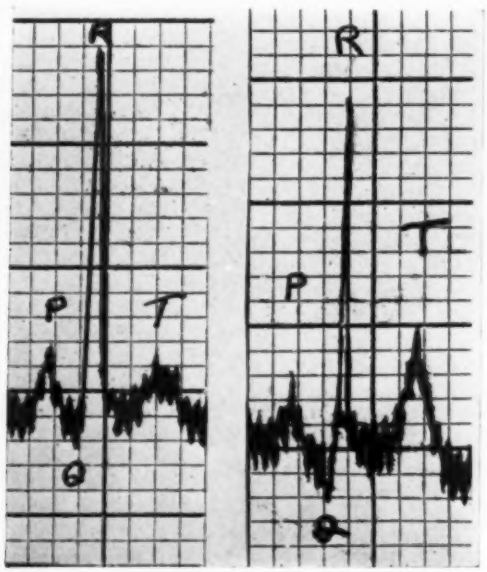

Fig. 3.—Control. 1 min. after 7 mg./kg. Aranthol.

Effect of Aranthol Given After Large Doses of Quinidine.—

In a previous study by one of us (Weisman[5]), the sublethal dose of quinidine, in dogs, was found to be 45 mg./kg. of body weight. This was the dose most frequently given by the intravenous route in the present experiments.

A pronounced fall in blood pressure, slowing of the cardiac rate, and depression of respiration followed the administration of quinidine. Respiration usually became very slow and shallow and in many cases finally ceased, which would appear to confirm the belief that clinical deaths caused by quinidine are frequently due to respiratory rather than cardiac depression (Barker and Levine[6]; Weisman[5]).

Nine of the dogs that first received Aranthol were given large doses of quinidine, injected over a period of one minute, after the blood pressure had returned to, or near, the preinjection level. Then, immediately after the blood pressure had dropped from an average normal of 120 mm. Hg or more, to about 40 mm. Hg or less, Aranthol was again injected, in doses up to 75 mg./kg. of body weight. In this group the average rise in blood pressure following the injection of Aranthol in the quinidine shocklike state was only about 20 mm. Hg; the pulse pressure increased only very slightly if at all. There was no beneficial effect on respiration.

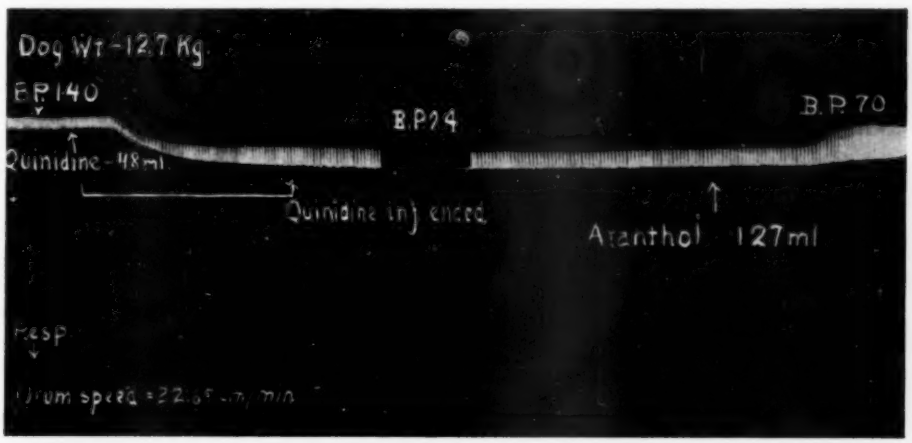

Fig. 4.—Dog No. 23, male, weight, 12.7 kg.; Aranthol, 10 mg./kg. following quinidine injection.

Quinidine was given to six dogs without any previous medication other than anesthetization. Aranthol was injected as soon as the animal was in a shocklike state as a result of this markedly vasodepressant drug. In this series Aranthol proved to be a very effective stimulant, particularly with respect to blood and pulse pressures (Fig. 4, Table II). The average rise in blood pressure after the injection of Aranthol was over 100 per cent, and the pulse pressure increased on the average to about twice the normal preinjection level. In two dogs, respiration appeared to be a little faster and deeper after the injection of Aranthol. In several experiments it was noted that repeated doses of Aranthol often produced a secondary tachyphylactic fall in blood pressure, manifested by a dip, as was observed by Jackson and by Walton and Brodie.

A typical fall in blood pressure frequently develops with repeated injections of many sympathomimetic drugs. It is possible that in the first group Aranthol produced a tachyphylactic reaction against itself when the second dose was given, after the quinidine injection.

The observations thus far may be summarized as follows: Normally there is a rise in blood pressure and an increase in pulse pressure following the administration of Aranthol. There is a marked drop in blood pressure and slowing of respiration after the administration of quinidine. When the administration of quinidine is preceded by an injection of Aranthol, the subsequent administration of Aranthol does not appreciably alter the depressant effect of quinidine. When Aranthol is not given prior to a large dose of quinidine, but only after, it appears to be very effective in counteracting the marked vasodepression induced by the quinidine, raising the blood pressure and increasing the pulse pressure.

TABLE II. EFFECT OF ARANTHOL GIVEN AFTER LARGE DOSES OF QUINIDINE

WEIGHT OF DOG (KG.)	QUINIDINE DOSAGE (MG./KG.)	BLOOD PRESSURE (MM. HG)		ARANTHOL DOSAGE (MG.)	B. P. (MM. HG)		AFTER ARANTHOL	
		BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE	AFTER*	PULSE PRESSURE†	RESPIRATION
12.7	24.6	140	24	10	24	108 in 5 min.	2+	No apparent effect
10.9	30.0	140	50	10	50	160 in 1 min.	2+	No apparent effect
9.5	45.0	140	0	10	0	70 in 8 min.	2+	Slight increased rate and depth
11.3	45.0	170	50	10	50	100 in 6 min.	±	No apparent effect
5.0	20.0	120	50	20	50	160 in 1 min.	2+	No apparent effect
13.6	26.5	120	40	22	40	130 in 1 min.	2+	Slight increased rate and depth

*Average rise in blood pressure after Aranthol, 85+ mm. Hg.
†Slight increase in pulse pressure is recorded as plus-minus; 2+ indicates the pressure was doubled.

Effect of Aranthol Plus Metrazol Following Large Doses of Quinidine.—

In a previous study in dogs it was found that Metrazol counteracted the depressant effect of quinidine, increasing the depth of respiration. In the present study, a combination of Aranthol (10 mg./kg.) and Metrazol* (20 mg./kg.) was given after the administration of large doses of quinidine. Results in five of the dogs are shown in Table III. There was a definite beneficial effect. The blood pressure rise was not as great as in the group in which Aranthol alone was used, but there was a greater increase in pulse pressure and a more favorable effect on respiration than when Aranthol alone was given after large doses of quinidine (Table III; Fig. 5). Leimdorfer,[7] in 1952 experimenting on dogs, felt that the beneficial effects of Metrazol and Aranthol on the cardiovascular disturbances occurring during Pentothal intoxication were "probably due to relief of the hypoxia induced by these drugs. Metrazol stimulates the respiratory center and improves the respiration significantly but has no direct effect on the heart itself. Aranthol, on the other hand, has a longlasting cardiotonic effect, increases the heart muscle action, elevates the cardiac output, and augments the coronary circulation but has no direct action on the respiration. The combination of these

*Aranthol and Metrazol in 10 per cent solutions.

drugs, by their synergistic action, achieves not only an improvement of the cardiovascular activity but also stimulates the respiration. This may be due to the direct action of Metrazol on the respiratory center and to the better blood supply of this center following the Aranthol injection."

TABLE III. EFFECT OF ARANTHOL PLUS METRAZOL GIVEN AFTER LARGE DOSES OF QUINIDINE

WEIGHT OF DOG (KG.)	QUINIDINE DOSAGE (MG./KG.)	BLOOD PRESSURE (MM. HG)		ARANTHOL-METRAZOL DOSAGE (MG.)	B. P. (MM. HG)		AFTER ARANTHOL-METRAZOL	
		BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE	AFTER *	PULSE PRESSURE†	RESPIRATION
11.8	45	140	0	Ar. 10; Me. 20	0	112 in 8 min.	2+	Increased rate and amplitude
10.0	32.5	170	40	Ar. 10; Me. 20	40	56 in 6 min.	3+	Increased rate and amplitude
10.0	45	220	60	Ar. 10; Me. 20	60	120 in 8 min.	2+	Not recorded
20.9	25	120	40	Ar. 10; Me. 20	40	98 in 7 min.	3+	Increased rate and amplitude
9.5	36	150	34	Ar. 10; Me. 20	34	64	2+	Increased rate and amplitude

*Average rise in blood pressure after Aranthol plus Metrazol, 55 mm. Hg.
†2+ indicates the pulse pressure was doubled; 3+ trebled, etc.

Effect of TA-20 (Aranthol and Theophylline) Following Large Doses of Quinidine.*—

Theophylline has been shown by Green and associates,[8] Starr and associates[9] and Folwell and associates[10] to be a very effective analeptic. It increases cardiac output and pulse pressure (Howarth and co-workers[11]; McMichael[12]). Its effect on blood pressure is not striking, but it increases the rate and depth of respiration (Sperling and co-workers[13]). Since the principal analeptic effect of Aranthol is on the cardiovascular system, a trial with a combination of the two drugs seemed advisable.

Seven dogs were used in this study (Table IV), and the average dose was 0.1 c.c. per kilogram of body weight. The outstanding effect of the administration of TA-20 after large doses of quinidine was on the pulse pressure and respiration (rate and amplitude) (Fig. 6; Table IV), evidenced in five of the dogs. In only two dogs was there any appreciable rise in blood pressure.

CONCLUSIONS

In experiments in normal anesthetized dogs, Aranthol in therapeutic doses proved to have pronounced cardiovascular stimulatory value, manifested by a rise of 100 per cent or more in blood pressure and a two-fold to six-fold increase in pulse pressure, which is probably indicative of increased stroke volume. The effect on respiration was not significant.

Electrocardiographic studies showed an increase in amplitude of the T wave and a slight increase in the Q-T interval. Toxicity was manifested by the appearance of extrasystoles.

*Each cubic centimeter of TA-20 contains 74 mg. of Aranthol base and 126 mg. of theophylline (Bilhuber-Knoll Corporation, Orange, N. J.).

TABLE IV. EFFECT OF TA-20 (ARANTHOL PLUS THEOPHYLLINE)* GIVEN AFTER LARGE DOSES OF QUINIDINE

WEIGHT OF DOG (KG.)	QUINIDINE DOSAGE (MG./KG.)	BLOOD PRESSURE (MM. HG)		TA-20 DOSAGE (MG.)	B. P. (MM. HG)		AFTER TA-20	
		BEFORE QUINIDINE	AFTER QUINIDINE		BEFORE	AFTER†	PULSE PRESSURE‡	RESPIRATION
8.6	32.3	160	38	120 Aran. 44 Theo. 76	38	80 in 10 min.	2+	Increased rate and amplitude
11.8	55	150	30	320 Aran. 117 Theo. 203	30	52 in 4 min.	3+	Increased rate and amplitude
8.18	62	162	30	180 Aran. 67 Theo. 113	30	32	0	No change
12.5	52	130	20	320 Aran. 117 Theo. 203	20	22	±	No change
11.8	37.5	130	18	300 Aran. 111 Theo. 189	18	102 in 4 min.	3+	Increased rate and amplitude
9.0	34.3	120	26	220 Aran. 181 Theo. 139	26	40	3+	Increased amplitude
10.4	56.2	126	26	280 Aran. 104 Theo. 176	26	no change	3+ in 25 sec.	Increased amplitude but died suddenly

*Each cubic centimeter of TA-20 contained 37% Aranthol base and 63% theophylline.
†Average rise in blood pressure after TA-20, 24 mm. Hg.
‡Plus-minus (±) indicates a slight rise in pulse pressure; 2+ indicates the pressure was doubled, 3+ trebled, etc.

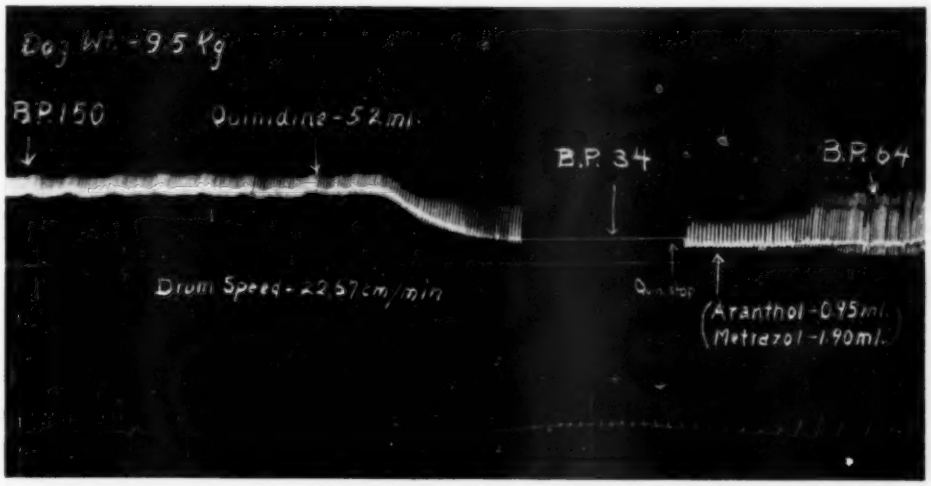

Fig. 5.—Dog; weight, 9.5 kg. Aranthol and Metrazol following quinidine injection.

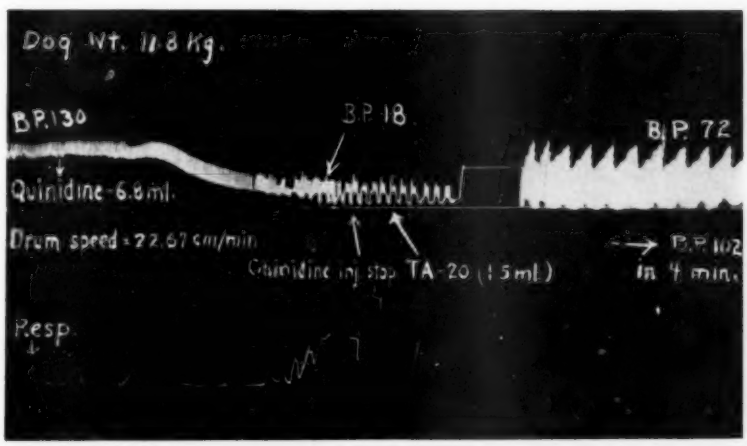

Fig. 6.—Dog; weight, 11.8 kg. TA-20 following quinidine injection.

As in other studies, the optimum therapeutic dose of Aranthol proved to be 4 to 10 mg./kg. of body weight. Doses larger than 10 mg./kg. were followed by toxic symptoms.

In severe vasodepression induced by large doses of quinidine, Aranthol alone or in combination with Metrazol or theophylline, given immediately after quinidine, proved to have effective analeptic properties. With the combination of Aranthol and Metrazol, given after large doses of quinidine, the over-all effect was more beneficial than was observed with Aranthol alone or the combination of Aranthol and theophylline, (TA-20), since in addition to the effect on blood pressure and pulse pressure, there was a respiratory-stimulating effect.

The authors wish to take this opportunity to thank Dr. Clinton H. Thienes of the Department of Pharmacology and Toxicology and Dr. Douglas R. Drury of the Department of Physiology of the University of Southern California for their valuable cooperation.

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A LINE-OPERATED DIRECT-COUPLED ELECTROCARDIOGRAPH

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RECENT evidence makes it increasingly apparent that the electrical cycle of the heart may not be complete at the end of the conventional segments of the electrocardiogram, such as the T or even the U wave, but that potentials of much slower evolution may be present. Bearing possible relations to the after-potentials of nerve, they may continue from beat to beat, forming an electrical bias with a variety of possible effects on the irritable behavior of the heart. There is some evidence that these factors become relatively more important when the metabolism of the heart is depressed and that they contribute to the allover electrocardiographic picture in these circumstances. It is equally obvious that modern electrocardiographic equipment is not suitable for the analysis of this problem. The different capacitors inherent in the construction of an AC amplifier impose time constants and phase shifts which mask or simulate the slow potentials sought. At the same time lack of visual control, electrostatic instability, and other technical difficulties have made the use of the string galvanometer practically impossible. The difficulties thus presented have been overcome with complete satisfaction in the direct-coupled electrocardiograph described here, which combines the merits of the string galvanometer with the simplified recording and the versatility of present-day AC amplifiers, maintaining a steady base line for a long period. It has been designed for recording with pen and ink photographic registration (Sanborn Cardiette) direct-writing with hot stylus (Beck-Lee Cardiall), and cathode-ray oscilloscope and camera (Dumont).

It is known that in a direct-coupled amplifier the main sources of drift, which find expression in instability and wandering of the base line, are the plate and filament voltages of the earlier stages, regardless of the design and internal arrangements of the components. To overcome this, the utilization of batteries for supply voltages has been necessary in the past. The first problem in design has therefore been to devise voltage regulators for plate and filament supplies operating directly from the 115-volt 60-cycle-power line to provide the necessary constant voltages within limits of normal variations in line voltage. Other limiting factors, in the operation of direct-coupled amplifiers are their rather special thermal characteristics. Accordingly, adequate consideration must be given to the rating of components and the ability of the amplifier system to reach thermal

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equilibrium with its surroundings, relatively quickly, and to maintain it despite long-continued operation. The use of a large and well-ventilated cabinet as the enclosure is consequently of considerable importance to insure that thermal factors do not cause undue electrical shifts. One of the most severe limitations in the long-term stability of direct-coupled amplifiers is the inherent gradual aging of components and tubes. The rate of variation here is dependent largely upon the factor of safety used or the over-rating of the size of the component for the actual function it is asked to perform. Components and tubes which have higher ratings than the operating conditions demand are much more stable and age less than those which under normal circumstances would be considered normally rated. Better quality components and those with low thermal coefficients are a necessity in the earlier stages of a direct-coupled amplifier.

Power Supply-Plate Voltage.—A variety of voltage regulators has been devised to provide stable direct voltages for plates with relatively low power consumption. The most popular and generally satisfactory is the series triode type controlled by an amplified difference signal. This takes the form of a power triode controlled by a pentode with a voltage reference tube in its cathode.

The plate-voltage power supply, which was employed here, is of this type and is shown in the circuit diagram of Fig. 1. Two modifications were made in the conventional circuit to increase the regulatory effect; one was to use a type 6AC7 (T*1.*) as the pentode amplifier instead of the usual 6SJ7, the other was to add a condenser CR to improve the transient regulatory characteristic. The operation of the regulator can be understood by referring to Fig. 1. A change of the regulated output voltage would vary the grid-cathode potential of vacuum tube *T1*, the cathode reference potential of which is maintained constant by a gaseous voltage regulating tube *T3*. Variation of the grid voltage of this tube (*T1*) will be amplified and affects the grid of the power tube (*T2*) in such a way as to produce a change in the voltage drop across it, opposing a change in the output voltage. In order to provide better transient regulation, the condenser CR is shunted from the positive supply voltage to the input grid of *T1*. For proper quiescent operation, this grid cannot be connected directly to the positive supply voltage. For maximum regulating effect, this grid must pick up as much of the disturbance in output voltage as possible, hence the addition of a large enough capacitor couples all the fluctuation of the output voltage into the regulatory system and still leaves the regulator with its necessary quiescent voltages.

Power Supply-Filament Voltage.—A newly developed photoelectric voltage regulator employing a saturable reactor as the controlling element was used to provide constant power for the filaments of the direct-coupled amplifier. This regulator is based on a principle similar to the load-responsive electronic regulator described by one of the authors.[1]

The operation of the regulator shown in Fig. 1 is briefly as follows: A gas-filled photo-tube, *T7*, is influenced by a small bulb, *A*, which is energized from the main 115-volts 60-cycle supply line. When the light of this bulb dims due to a decrease in the line voltage, less light falls upon the photo-tube. The resultant decrease in photocurrent decreases the plate current pulses of pentode *T4*. This plate current consists of positive pulses which are transmitted through transformer

TR4 to diode *T5*. The decrease in plate current pulses of the pentode results in a decrease of rectified voltage of the diode *T5*. This in turn decreases the negative direct potential applied to the grid of the thyratron *T6* and causes an increase in its plate current. The DC winding of a saturable reactor *SR* is located in the cathode circuit of the thyratron *T6*. The AC winding of the saturable reactor is connected in series with the power transformer *TR3*. As the thyratron plate current rises due to a decrease in intensity of light falling on the photo-tube, the reactance of the AC winding of the saturable reactor decreases. The ratio of voltages across the primary of the transformer to the voltage across the AC winding of the saturable reactor increases, and the voltage across the primary of the transformer increases in proportion, raising the voltage across the secondary. When the light intensity of the bulb increases due to an increase in the line voltage the reverse process occurs.

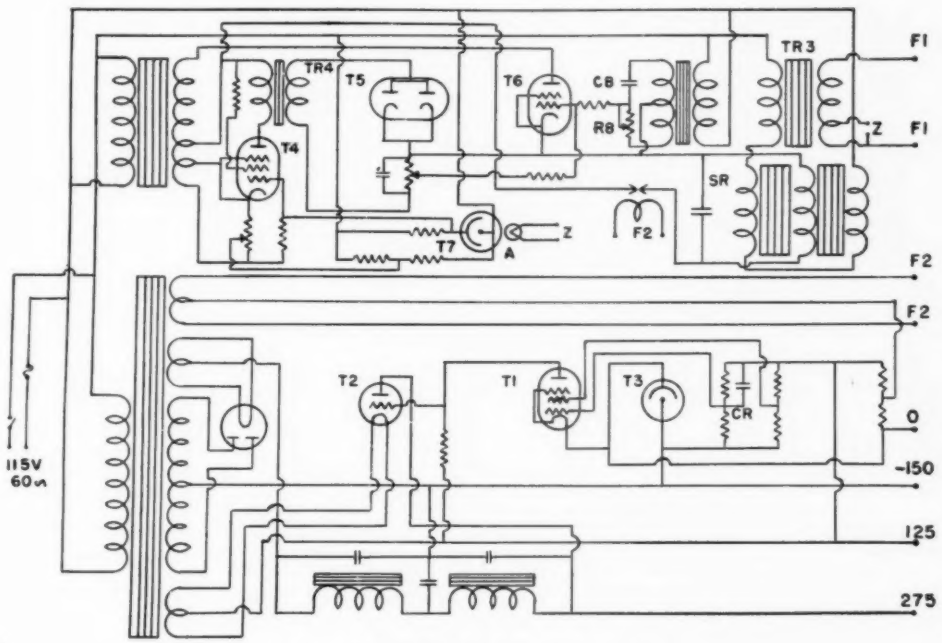

Fig. 1.—Circuit diagram of power supplies.

In order to set the mean value of filament voltage, a variable resistance *R8* in series connection with a fixed capacitor *C8* constitutes a phase-shift bridge which is employed to control the mean bias of the thyratron (*T6*). From this, an AC control voltage of determined phase is derived and applied to the grid of the thyratron. This setting determines the value of steady current flowing through the DC winding of the saturable reactor which in turn determines the mean value of the constant voltage which is applied to the filament. From different taps of the regulated secondary of transformer *TR3*, voltages are taken for the filaments of the tubes of the regulator *T4*, *T5*, *T6*, and for the bulb influencing the photo-tube.

Amplifier Circuit.—The direct-coupled amplifier described here is essentially a three-stage push-pull, balanced type with a very high amount of in-phase degeneration (Fig. 2). The components entering into the construction were carefully chosen and operate very far below their normal ratings. The tubes were also carefully chosen to have balanced characteristics and operate with very low plate currents. An additional advantage in incorporating large in-phase degeneration and using balanced tubes results in the amplifier not only being insensitive to external interference but puts a less severe requirement on the stability of the plate-supply voltage. Irregularities in the plate-supply voltage are in-phase signals which are discriminated against by the push-pull amplifying stages.

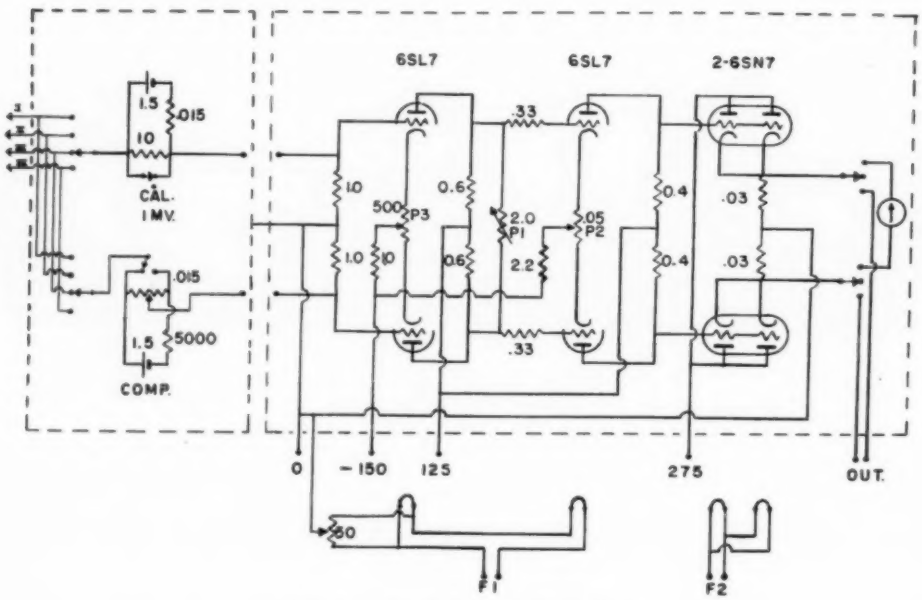

Fig. 2.—Circuit diagram of amplifier.

The amplifying channel itself consists of two 6SL7GT double-triode tubes, directly coupled in cascade. These are coupled to two 6SN7GT tubes, push-pull parallel connected as a cathode follower output stage. This arrangement gives adequate gain and a low enough output impedance to operate a recorder directly. The output of the amplifier is fed through a double-pole triple-throw switch. This switch connects the amplifier to a neutral off position for warm-up, a panel meter for preliminary adjustments, or the recorder for registration of the potentials under study.

Operating Characteristics.—The operation of the amplifier can be followed by referring to Fig. 2. The balance of the input stage is controlled by a screwdriver-adjust potentiometer *P3* located between the cathodes of the first stage. The balance of the second stage which is the main centering control, *P2*, of the amplifier is similarly located in the second stage cathodes. The gain or sensitivity control, *P1*, is located between the plates of the first stage. With this arrangement, the gain and centering of the amplifier can be adjusted independently.

To accomplish this feature in operation, the gain control, *P1*, is reduced to zero and the output balanced with the main centering control (*P2*). The gain control (*P1*) is then turned to maximum and with no input signal the output is rebalanced with the first stage screwdriver-adjust potentiometer, *P3*. The amplifier is now balanced so that varying either the gain control or centering control does not cause interference one with the other.

The input into the amplifier is fed from a lead selector box containing a calibrating voltage and a bucking or compensating voltage. The usual one millivolt calibration voltage appears in series with the subject. The compensating voltage is adjustable from zero to one volt of either polarity and is also injected in series with the subject. This compensating voltage is necessary to eliminate polarization and other potentials encountered.

Fig. 3.—Calibration with 1 mv. input, photographic recording.

Recording Systems.—When first employed, the direct-coupled amplifier was used in conjunction with a Sanborn Cardiette photographic-recording galvanometer. A direct viewing of the record as it progressed was made by parallel connection of the Sanborn Cardioscope. Due to the limited amount of record displayed by the cardioscope and the inconvenience of viewing the record in semidarkness, a direct-writing system was found necessary. To accomplish this, a standard Beck-Lee electrocardiograph was used in connection with the direct-coupled amplifier described here. Connection was made from the output of the direct-coupled amplifier to the grids of the last voltage-amplifying stage of the Beck-Lee amplifier. This gave a direct-coupled recording from the input of the amplifier to the recording stylus. Although a Beck-Lee electrocardiograph was used, most standard electrocardiographs are direct-coupled in the last stages and similar connections could be made. For oscillographic recording direct connection was made to the input of Dumont Type 279 oscilloscope with a recording camera attached.

Performance.—The apparatus as a whole has proved very useful and versatile. With the cardiette and cardioscope, the sensitivity available was one millivolt per centimeter and the frequency response was limited only by the speed of the recording galvanometers, extending from zero to this limitation. With the Beck-Lee direct-writing recorder the upper frequency was limited only by the pen writer. The over-all sensitivity available was one millivolt per three-quarters

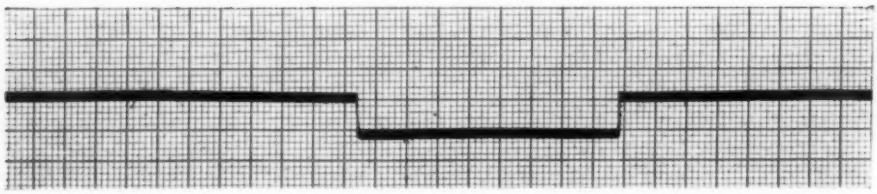

Fig. 4.—Calibration with 1 mv. input, hot-stylus recording.

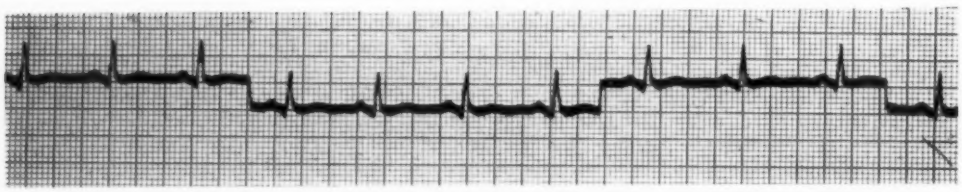

Fig. 5.—Electrocardiogram, Lead II, with superimposed calibration, hot-stylus recording.

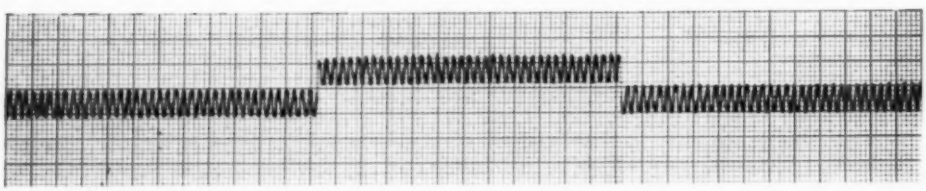

Fig. 6.—Superimposed sinusoidal waves, with 1 mv. calibration. Hot-stylus recording.

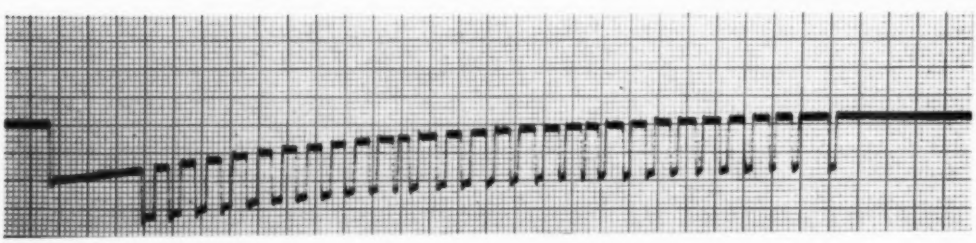

Fig. 7.—Record from conventional electrocardiograph, 1 mv. steady signal with superimposed DC impulses.

of a centimeter. With the Dumont Oscilloscope the limitations were those of the direct-coupled amplifier described here. A frequency response flat from zero to 5,000 cycles and attenuated by 50 per cent at 12,000 cycles was obtained. The noise level, principally from the input tube heaters, is of the order of a tenth of a millivolt.

To illustrate the response of the apparatus to various wave forms, tests were made with various synthesized waves. Figure 3 shows the square-wave calibration obtained with the photographic recording galvanometer. Figure 4 illustrates the same with the direct-recording Beck-Lee hot-stylus recorder. Figure 5 shows the superimposition of the calibration wave on an electrocardiographic tracing. Figure 6 shows the addition of two waves of approximately 1 millivolt peak amplitude, one being a direct potential and the other a sinusoidal wave. Figure 7 shows the effect produced when a direct potential is added to a pulsating potential, when a conventional AC amplifier electrocardiograph is used. It is to be observed that the base line decays back to its original position in spite of the maintenance of the direct input potential.

Fig. 8.—Photograph of instrument.

Figure 8 shows the complete apparatus containing the power supplies and amplifying stages. The input connection appears on the center of the front panel while the output is at the rear. The panel meter monitors the output of the amplifier, and its switch is located above it. The input lead-selector box containing the calibrating and compensating voltages is not shown.

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AN IMPROVED FLARIMETER

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NEWARK, N. J.

MEN of large frame are expected to exceed average weight for their height. Their lung capacity should be in proportion also, so a table of normal vital capacity by height gives a valuable correction factor for estimating true overweight. To measure vital capacity the tank spirometer has been used, which is inconvenient in practice. A more portable instrument* is the new flarimeter.[1] So small that it can be tucked into pocket or bag, adding only 66 grams (1/7 lb., including mouthpiece and rubber tubing) to the aneroid used for blood pressure, and both together weighing but one-half a pound, it measures vital capacity with an average error of less than 2.5 per cent.

A photograph of the latest model is shown at the top of Fig. 1, with a drawing of the orifices below. The pressure gauge used is a sphygmomanometer aneroid. It is attached to the compression chamber (*C*) of the flarimeter by means of a quick-changing device, a hollow tube (*M*) projecting at right angles to the direction of air flow with its outer surface tapered to fit into the opening of the manometer. A simple twist attaches them together airtight.

The subject blows through the mouthpiece (shown in the upper right-hand corner) into the rubber tube and out through the large orifice (*L*) as a nozzle. Orifice and chamber are machined from one piece of metal. The outer surface of the nozzle is tapered so that an accessory standard small orifice (*S*) can be quickly attached. It limits the flow of air to 36 c.c. per second with the gauge at 20 mm. When detached, the large orifice limits the flow to 200 c.c. per second at the same pressure.

Previous models used valves, the lubricants of which contaminated the orifices, producing errors in flow. The present model is not only free from this defect, but it also avoids a temperature correction because its heat capacity is so small. The flarimeter reads the same at all ordinary room temperatures, with an average deviation of a single calibration of 1.3 per cent.

Figure 2 depicts a vital-capacity blow. The examiner is watching the gauge to make sure that the pressure is held exactly on 20. He has the stop watch in hand, to snap the length of blow. If it reads 20 seconds, the vital capacity is 4 liters, if 25 seconds it is 5 liters, that is, the formula is Vital Capacity (liters) = 0.2 × Length of Blow (seconds). Any blow below normal vital capacity is real evidence of either perfunctory performance, slight build, or physical defect. Once a person has acquired the simple skill needed for maximum inspiration, further practice does not yield much increase in vital capacity. After age forty it decreases about 0.5 per cent per year.

From the Medical Department, Prudential Insurance Company of America.

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*The flarimeter is manufactured by Becton, Dickinson and Company, Rutherford, N. J. A manual is furnished with the instrument giving tables and details.

Fig. 1.—Photograph of flarimeter, manometer, and small orifice attached. Below: Section showing large orifice (*L*); small orifice (*S*) detached.

Fig. 2.—A vital-capacity blow.

The accessory small orifice (*S*), shown in Fig. 1, plugs on quickly over the nozzle of the large orifice as in the photograph. It is used to keep the pressure on the heart constant. It reveals any attempt at breath-snatching, and so obviates the need for a nose clamp. Shortness of breath is one of the earliest symptoms of circulatory impairment. While exercise enough to produce breathlessness is an excellent measure of shortness of breath, it is not always advisable to push the test that far. Blowing through the small orifice tells much the same story and has the advantage of quick recovery. This blow is equivalent to holding the breath under reproducible conditions.

While the longest flarimeter blow by an individual is the simplest good measure of his breath-holding ability, it suffers from two disadvantages. First, it depends on the will of the subject. He must decide when to stop. The examiner can only guess why. The second disadvantage is the risk in blowing too long. It is not always safe to hold the breath until the systolic blood pressure rises above 200 mm. Hg. It is, therefore, advisable to follow the systolic blood pressure during the blow, which requires another pressure gauge. One is for the flarimeter and one for the sphygmomanometer. Stopping the blow when the systolic pressure has risen 30 mm. gives the length of blow (T_{30}) as a "flarimeter tolerance." Such tolerances are the best measures of shortness of breath.

A standard flarimeter blow can be given immediately after standard exercise,[2] to measure the breathlessness produced by the exercise. If a direct-writing electrocardiograph is available, it can be used to obtain a continuous record of the heart rate during this blow. After it the rate drops abruptly to a minimum, usually below the rate before exercise, giving an S-T depression as a test of coronary insufficiency which is more reliable than that after exercise alone, for an increase in heart rate in itself is known to depress the S-T junction. College male athletes show a powerful vagus slowing of the heart after a 30-second blow begun 10 seconds after standard exercise, an appreciable number having extrasystoles during, at the end, or just after this blow.

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Clinical Reports

PULMONARY ARTERY THROMBOSIS SIMULATING PULMONIC VALVE STENOSIS WITH PATENT FORAMEN OVALE

E. Grey Dimond, M.D., and T. Reid Jones, M.D.

Kansas City, Kan.

WE HAVE recently seen a case with signs and symptoms very like those noted in the syndrome of congenital pulmonary stenosis with subsequent shunting from right-to-left through the foramen ovale. At autopsy it was discovered that the cause for the obstruction to pulmonary flow was not a congenital stenosis but a thrombosis which had evidently risen in situ and had obstructed the right and left main stem pulmonary arteries. The foramen ovale was wide open.

CASE REPORT

R. F. (KUMC Case No. 178976), aged 25, white, was first seen at the Kansas University Medical Center, March 18, 1951, complaining of shortness of breath on exertion of five months' duration.

His previous health had been excellent. Birth and developmental history were normal. He had participated in varsity high school athletics. From 1944 to 1946 he served an enlistment in the Navy. His only recent illness had been an uncomplicated attack of tonsillitis in 1947. Six months before admission, and prior to onset of symptoms, he left a job which involved lifting 100-pound sacks into a truck. When first seen he was working as a machine operator but was quitting on account of his symptoms.

The shortness of breath had increased steadily since its onset 5 months earlier and about 3 months prior to his admission he noted that his lips and fingers were blue. In the past month his fingers and toes had begun clubbing. He also complained of left chest pain, made worse by exertion.

Physical examination showed an alert man in good nutrition. Dyspnea was produced by walking a few steps. There was moderate cyanosis of mucosa and nail beds, and minimal clubbing of the fingers and toes. Blood pressure was 120/90 mm. Hg and pulse 85. Inspection of the chest was negative; the heart was not enlarged to percussion. The pulmonary second sound was not accentuated. A Grade 5 systolic murmur was heard, maximal at the pulmonic area and widely transmitted over the left hemithorax and to the suprasternal notch. The liver edge was palpated one fingerbreadth below the right costal margin. The peripheral pulses were normal. The legs showed no evidence of venous thrombosis. The rest of the physical examination was negative.

From the Department of Medicine, University of Kansas Medical Center, Kansas City, Kan.
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Laboratory examination: Erythrocytes were 5,840,000 per cu. mm., hemoglobin 16.0 Gm. per cent, leukocytes 15,800 with differential count as follows: Neutrophils 78 per cent, lymphocytes 18 per cent, monocytes 3 per cent, eosinophils 1 per cent. The sedimentation rate (Wintrobe) was 5 mm. per hour. Blood: Wassermann and Kahn tests were negative. Urinalysis showed a specific gravity of 1.003, 1.004, 1.014; a trace of albumin, no sugar and 1 to 3 pus cells per highpower field in the centrifuged sediment. Blood chemistry determinations on April 1, 1951 were as follows: nonprotein nitrogen, 34 mg. per cent; creatinine, 1.5 mg. per cent; sugar, 69 mg. per cent; sodium, 139 meq. per liter; potassium 4.6 meq. per liter; chlorides, 108 meq. per liter; prothrombin time was 78 per cent of normal.

A roentgenogram of the chest (March 8, 1951) revealed the following: . . . "the left pulmonary artery is full but the lung vascular markings are not prominent. The right ventricle is enlarged, numerous segments of fibrosis are seen in the lungs, especially in the right mid-lung field and right apex." Fluoroscopy established the presence of quiet hilar shadows and clear lung fields.

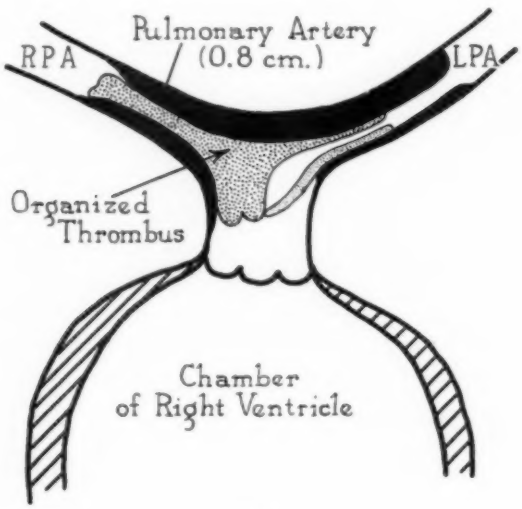

Fig. 1.

Angiocardiograms of March 22, 1951, were interpreted . . . "findings are those of pulmonary stenosis. Localization of the stenotic area is considered to be at the valve cusp, although this is not as definite a finding as I would like."*

The *electrocardiogram* of March 1, 1951, included six limb leads and V leads across the chest from right to left axilla. Interpretation: "Prominent R wave over right chest with intrinsicoid deflection delayed to 0.06 seconds. Considered indicative of right ventricular hypertrophy."

Measurement of oxygen used per minute in inspired air, according to the method of Bing revealed the following: 3.2 per cent of oxygen used at rest; 2.8 per cent of oxygen used during exercise. This was considered as evidence of decreased pulmonary blood flow.

In view of these findings, it was felt that the patient had some obstruction to pulmonary flow and from the location and characteristics of the murmur, that the obstruction was a pulmonary stenosis, congenital in origin. It was assumed that his present difficulty of dyspnea, cyanosis, and clubbing was due to increasing pressure in the right auricle and subsequent opening of his foramen ovale, with functional flow from right-to-left.

*Interpretation by: Dr. Donald Germann.

Because of his increasing limitation, it was decided that a pulmonary valvulotomy was his only chance for recovery. Therefore, on April 5, 1951, a left thoracotomy was done. After about 40 minutes of dissection, the cyanosis deepened, the pulse became irregular and the patient expired.

Autopsy: The entire right pulmonary artery was occluded by a thrombus. The left pulmonary artery was practically entirely occluded by the same process except for a small channel. The thrombus extended down to the pulmonary valve. The thrombus was not new, but was undergoing organization. The foramen ovale was widely patent (Fig. 1).

Approximately 30 minutes after the patient's death, a young woman appeared at the hospital and supplied the following history: She and the patient had been in an automobile accident approximately 5 months before the operation. The young man was driving when the car struck a tree, and the patient's chest was severely bruised against the steering wheel. For several days after the accident the patient's chest was bruised and inspiration was difficult.

DISCUSSION

In retrospect, the correct diagnosis in this case might have been made if the history of the automobile accident had not been withheld. Nonpenetrating trauma to the chest wall can produce tears, perforations, and contusions. The patient had evidently been in excellent health prior to 5 months before his death, as evidenced by participation in high school athletics and serving 3 years in the navy. One month after an auto accident he noted effort dyspnea which progressed rapidly to an inability to walk more than a few feet. About 3 months before death, increasing cyanosis was noted which probably coincided with the functional opening of the foramen ovale. It seems reasonable to postulate the nonpenetrating trauma as the possible antecedent cause for the in situ thrombosis, and this might have alerted us to the possibility that an obstructive lesion was present.

The clinical findings were not unlike those noted in pulmonary stenosis with patent foramen ovale. The angiocardiogram correctly indicated an obstruction at the pulmonary valve site. Unfortunately, this was interpreted as stenosis of the valve. The measurement of the ratio oxygen utilization to total air ventilation before and after exercise indicated a decrease in pulmonary flow. Here again this was interpreted as evidence of valvular stenosis. Catheterization was not done.

SUMMARY

A 25-year-old man presented a history of dyspnea and cyanosis of increasing degree beginning 5 months prior to hospitalization. A harsh systolic pulmonary murmur and right ventricular hypertrophy were present. Angiocardiograms indicated obstruction at the site of the pulmonary valve. At autopsy, a large organized thrombus, totally blocking the right pulmonary artery and partially blocking the left and main artery, was found. The foramen ovale was widely patent. A history of severe anterior chest trauma, occurring 5 months earlier, was obtained.

ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH ACUTE PORPHYRIA

LOUIS F. ALBRIGHT, M.D., F.A.C.P., AND FRANK J. BROWN, M.D.

POINT PLEASANT, N. J.

ACUTE porphyria is a disease of disturbed pigment metabolism, constitutional or toxic, characterized by abdominal pain, nervous and mental symptoms, and the excretion of large amounts of porphyrins in the urine. Although the presenting complaints are often sudden in onset, the disorder appears to be inborn and the metabolic disturbance is found even in the absence of acute symptoms. The disease is familial and has been observed in three generations, being inherited as a Mendelian dominant.[1]

L. M. A 35-year-old white letter carrier, was perfectly well until Dec. 9, when he was awakened at 3:00 A.M. with severe precordial pain radiating to his right shoulder, diaphoresis, nausea, and vomiting. On examination at that time the patient was ash-white with moist and clammy skin. His blood pressure was 120/80 mm. Hg when first taken and ten minutes later was 100/65 mm. Hg. Pulse was 120 and regular. He was given Demerol, and seven hours later an electrocardiogram was taken which showed strongly suggestive signs of a recent posterior wall myocardial infarction, i.e., depression of the RS-T segments in Leads I, aV_L and left-sided precordial leads and RS-T segment elevation in Leads II, III, and aV_F.The patient was then hospitalized at the Point Pleasant Hospital. He had slight diarrhea the morning of admission. He was treated with 100 mg. Demerol which relieved his substernal distress. He was also put on anticoagulant therapy consisting of Depo-Heparin Sodium, 200 mg. every 18 hours. He received Nembutal, 1½ grains at bed time. His temperature rose on the second day to 100.4° F. and maintained a plateau until the fourth hospital day when it gradually subsided. A repeat electrocardiogram taken on Dec. 10 showed the presence of significant Q waves in Leads II, III, and aV_F and tendency to inversion of the T waves in the same leads. This finding confirmed the diagnosis of a recent posterior wall myocardial infarction. The patient did very well from a clinical standpoint and on the fourth hospital day had no complaints whatsoever. Since the patient was young and quite active in bed and also showed no evidence of shock at that time, anticoagulant therapy was discontinued. On the sixth hospital day, having been previously well for two days, the patient began to complain of nausea and epigastric distress. His temperature became elevated to 101.8° F. and his blood pressure was now 150/110 mm. Hg. His white count showed a leukocytosis of 12,700 with 87 per cent polymorphonuclear. He then began to complain of severe abdominal pain without distension, tenderness, or rigidity. The pain could not be controlled completely even with Demerol and Methadon. He was given Banthine, phenobarbital, and papaverine, ineffectively. A repeat electrocardiogram on Dec. 17 showed no evidence of recent activity or reinfarction. At that time the patient voided a specimen of urine that was the color of Burgundy wine. His admission urinalysis was clear amber and otherwise normal. A Schwartz test done on Dec. 19 was reported as strongly positive for prophyrins. A

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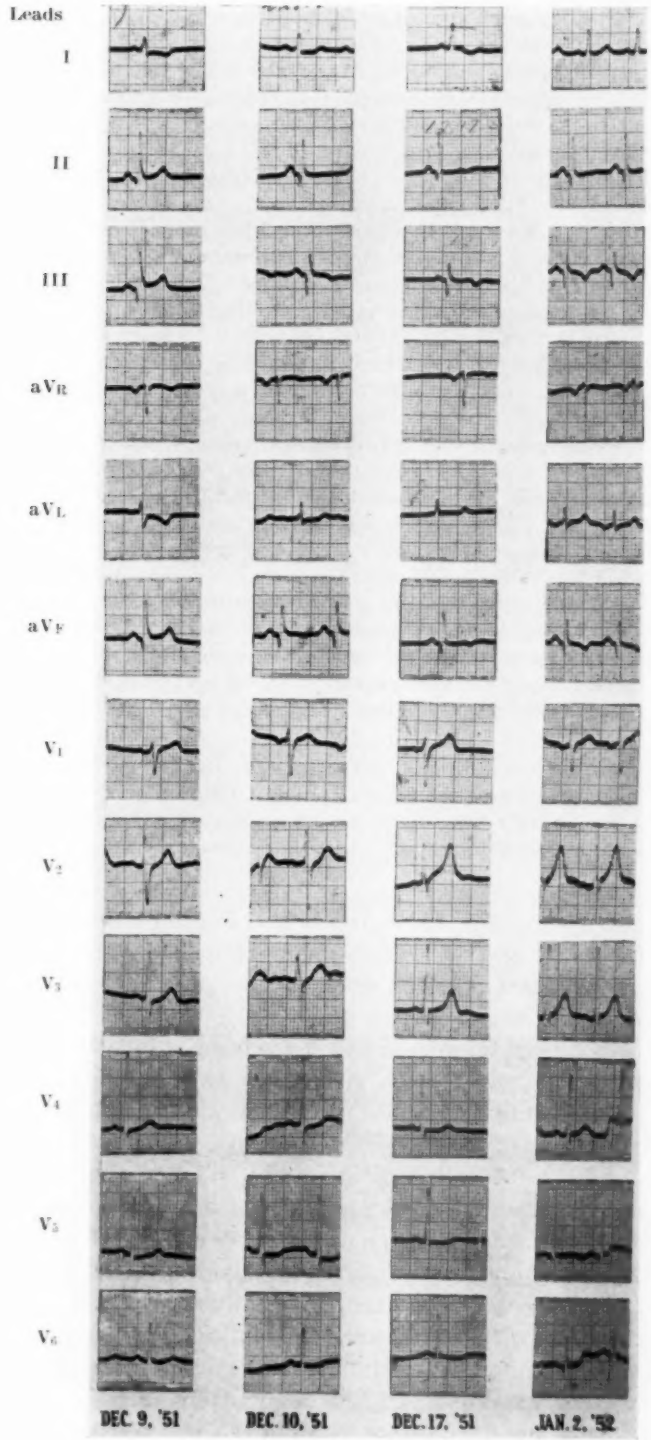
Leads
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
DEC. 9, '51
DEC. 10, '51
DEC. 17, '51
JAN. 2, '52

Fig. 1.

twenty-four hour urine specimen and a sample of the patient's serum were sent to Dr. Cecil J. Watson at the University of Minnesota for quantitative analysis. It was reported that it contained very large amounts of uroporphyrin, 26,180 micrograms per day, also 42 units of porphobilinogen, and 310 micrograms of coproporphyrin. The serum coproporphyrin value was distinctly elevated at 1.8 micrograms per 100 c.c. Normally, it cannot be demonstrated at more than 0.5 micrograms at the most and usually none. These findings were reported by Dr. Watson as being entirely characteristic of porphyria. After the diagnosis of acute porphyria was made, all medication was withdrawn. The patient continued to have severe abdominal pain which was girdle-like and later traveled down to both testes. The patient complained bitterly and became very difficult to manage. Since it is known that phenobarbital and other drugs aggravate this condition, they were withheld and sedation was confined to paraldehyde and Methadon. The patient's appetite was markedly diminished but vomiting stopped. Constipation was present which was not relieved by milk of magnesia and only slightly by repeated enemas. Since the pain resembled that due to radiculitis, it was thought advisable to start a course of massive vitamin B_{12} injections since recent work has indicated that it may be effective in cases of intractable neuritis. However, before therapy with vitamin B_{12} was instituted, the patient showed some signs of improvement. He was started with daily doses of vitamin B_{12}, 1,000 mg. daily for twelve days. He was discharged from the hospital on Dec. 24 and remained at bed rest at home while receiving the vitamin B_{12} therapy. He gradually improved but still complained of marked weakness and sensitivity of the skin to ordinary touch. He had marked intention tremor of both hands and also showed evidence of vasospasm of both upper extremities. His hands were pale and cold. Hemoglobin was 16.0 Gm. His blood pressure continued to remain slightly elevated, 140/95 mm. Hg, but his temperature subsided. After a lapse of about five days, another course of vitamin B_{12} was given. The patient improved progressively and has gained weight and strength. Examination of the urine one year after the onset of his acute attack was positive for porphyrins. At present, the patient works full time as a letter carrier and is without complaints. A repeat Schwartz test in May, 1953 was only faintly positive for porphyrins.

Family history reveals no evidence of porphyria. His father died at an early age of influenza. His mother is living and has diabetes. He has one brother and one sister, who are living and are well. On careful questioning the patient has had no illnesses in the past but has noted that on occasion the urine has been dark. However, it has never resembled the Burgundy-colored urine he voided at the onset of symptoms.

DISCUSSION

Since the patient had no symptoms or signs suggestive of porphyria on admission, a Schwartz test was not done on his admission urinalysis. However, nothing grossly abnormal was noted about its appearance. It seems likely that this patient was suffering with latent porphyria which became manifest as a result of an acute coronary occlusion together with the usual drugs used in the treatment of that condition. However, cardiovascular changes are often quite prominent in cases of acute porphyria. A rise in blood pressure is noted as well as a tachycardia. Vasospasm is usually present and was evident in our patient soon after the onset of symptoms. It is thought that the neurological signs and symptoms are due to an ischemic degeneration of the nerve fibers.[3] It is conceivable that porphyria may have played a role in the causation of the acute coronary occlusion. Since there is no known specific treatment for acute porphyria except to withhold medication which is known to make it worse, vitamin B_{12} was instituted. It is difficult to evaluate the response of this patient to massive doses of vitamin B_{12}. The results were certainly not dramatic. He began to improve a few days before vitamin B_{12} was instituted and his improvement continued slowly but progressively.

SUMMARY

A case of acute myocardial infarction followed by symptoms and signs of acute porphyria is presented. While it is probable that the acute myocardial infarction caused latent porphyria to become manifest it is possible that the underlying disease may have been due to porphyria.

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RIGHT VENTRICULAR STENOSIS OF THE BERNHEIM TYPE IN A CASE OF SEPTAL INFARCTION

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LISBON, PORTUGAL

IN SPITE of some controversy, it seems that Bernheim's syndrome is a true clinical entity, with possible diagnosis during life. Among the papers dealing with the subject, the reports of Podesta,[1] Martini and Joselevich,[2] Russek and Zohman,[3] Atlas and associates[4] are convincing upon the correlation between the clinical picture and the pathologic findings.

Bernheim's syndrome in its pure form is a right ventricular stenosis due to a great hypertrophy of the left ventricle with a bulging septum. Usually the situation is the result of a common disease leading to this hypertrophy, most of the cases being essential hypertension or aortic stenosis. However, on theoretical grounds, any alteration leading to a bulging septum, protruding into the right ventricle, can produce the same clinical picture. As a matter of fact, a ventricular neoplasm,[5] or a septal infarction,[6] produces a classical picture of diastolic failure of the right ventricle, with venous engorgement and liver engorgement, free of pulmonary congestion. This bulging of the septum in myocardial infarction is pointed out in the pathologic data of Myers and associates.[7]

The following case seems to be one more of this right ventricular stenosis due to septal bulging.

CASE REPORT

A.M.S., a 43-year-old man, came in the hospital complaining of excruciating chest pain, dizziness, and cold sweat.

Past history revealed a typical effort angina beginning six years ago, followed two weeks later by a prolonged attack of pain lasting many hours. Following this attack, he experienced some crises of pulmonary edema. He took digitalis and recovered completely, working hard in the last five years. He thought he had acquired syphilis twenty-two years ago, but never was treated.

On admission the patient appeared apprehensive, with slight cyanosis but no dyspnea. The cervical veins were fully distended. Blood pressure was 110/64 mm. Hg, the pulse was regular, 88 beats per minute, the heart sounds were poor; there was a faint diastolic murmur in the right second and third intercostal spaces. The pulmonary auscultation was normal. The liver edge was palpable two fingers below the right costal margin. There was no edema. The electrocardiogram showed left bundle branch block, with a V_4 pattern of acute myocardial infarction and a Q wave in V_6 and aV_L leads (Fig. 1). The Wassermann and Kahn tests were positive.

During the first two weeks the usual therapy of bed rest and anticoagulants was prescribed. After a gradual improvement, the patient became oliguric and increasingly cyanotic, developing a slight pitting edema of the sacrolumbar region. The liver became more congested and the cervical veins more turgid. In spite of full digitalization and mercurial diuretics, the signs of

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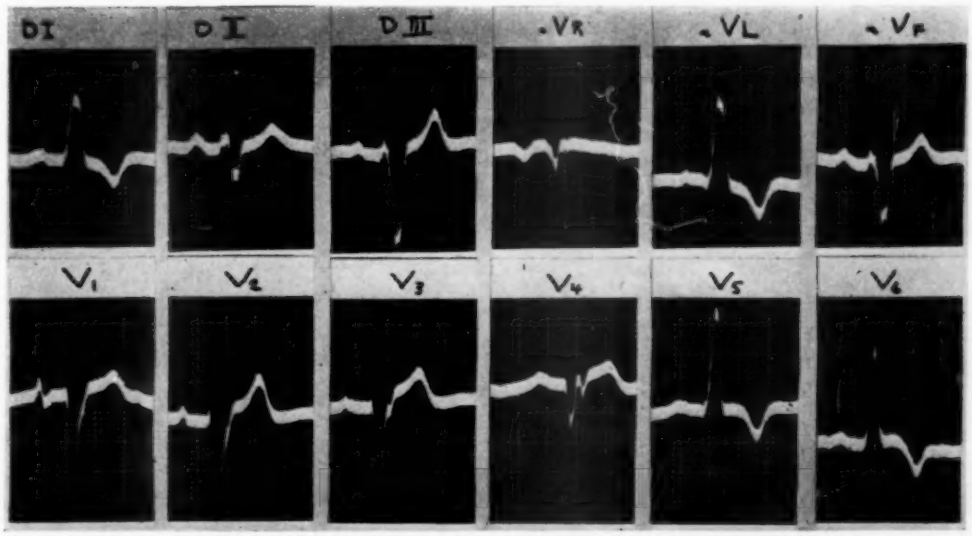

Fig. 1.—Left bundle branch block with septal infarction.

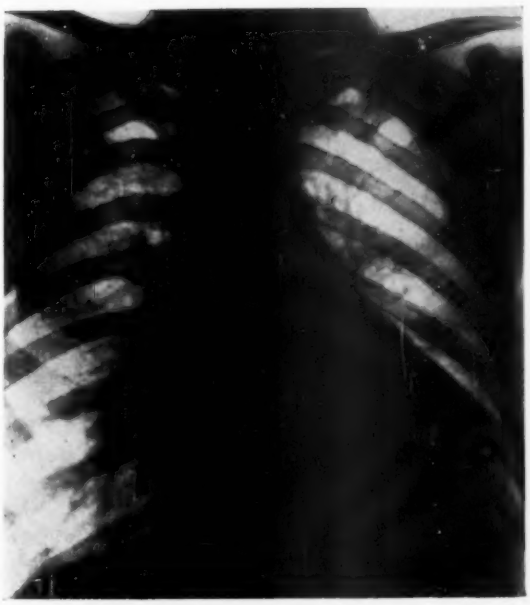

Fig. 2.—Enlargement of the left ventricle and absence of pulmonary congestion.

congestive heart failure progressed rapidly. He developed anasarca with ascites. The electrocardiogram remained unchanged. No lung congestion was found either clinically or radiologically. The roentgenogram showed an enlarged heart with pronounced left ventricular dilatation, but the signs of pulmonary engorgement were minimal (Fig. 2). The patient died three months after admission.

The clinical diagnosis was: Syphilitic aortitis, coronary insufficiency, old myocardial infarction, recent infarction with involvement of the septum, ventricular aneurysm, Bernheim syndrome.

Fig. 3.

Fig. 4.

Fig. 3.—Left ventricle showing infarction of the free wall and the septum and mural thrombosis.

Fig. 4.—Transverse sections of the ventricles showing the bulging of the septum and the right ventricular stenosis.

Necropsy Report.—No fluid was found in the pericardial and pleural cavities, but the abdomen contained 500 c.c. of clear fluid. The heart was greatly enlarged, weighing 775 grams. The apex was thin walled and round, formed by the left ventricle. On the epicardial surface many small hemorrhages were seen. There was a conspicuous dilatation of the pulmonary conus and right auricle. There was a tremendous dilatation of the left ventricle with a bulging septum protruding into the right ventricular cavity, which, in the lower one-half, was reduced to a mere virtual chamber. The anterior wall of the left ventricle, near the apex, was transformed into a fibrous scar. The upper one-half of the septum was also fibrous. The lower one-half showed a fresh infarction with a mural thrombus (Fig. 3).

Transverse sections were made 3 cm., 5 cm., and 7 cm. below the base (Fig. 4). The thickness of the wall of the left ventricle was similar everywhere, around 1.3 cm. thick. The septum was thicker and curved. The right ventricular cavity was sickle shaped and small. There was a syphilitic aortitis with valvular incompetence, few atheromatous patches, and old occlusion of both branches of the left coronary artery.

The lungs were reddish, slightly firmer than the normal, with no edema or bronchopneumonic foci.

The liver (28 × 19 × 8 cm.) had the typical nutmeg appearance.

On microscopic examination, sections of the heart showed a healed infarction of the anterior free wall of the left ventricle and upper part of the septum and a more recent infarction of the lower septum.

The anatomic diagnosis was: (1) syphilitic aortitis with aortic insufficiency; (2) coronary atherosclerosis, with occlusion of the left coronary artery and myocardial infarction; (3) hypertrophy and dilatation of the right auricle with compression of the right ventricle by a bulging septum (Bernheim's Syndrome); (4) ventricular aneurysm; (5) chronic passive congestion of the spleen, kidneys, and liver.

DISCUSSION

The typical history of coronary failure on two different occasions allows the diagnosis of two separate myocardial infarctions, the second confirmed by an electrocardiogram. In fact, the only instance in which such electrocardiographic diagnosis can be made in the presence of left bundle branch block is when the entire septum is involved. So, we can be sure of the existence of a recent septal infarction. The persistence of a S-T displacement, lasting more than two months, is in favor of a cardiac aneurysm.

The evolution to an intractable right-sided congestive failure, free from pulmonary engorgement, poses another diagnostic problem. We can ascribe this failure to a bulging septum (actually, a septal aneurysm) or to a septal perforation. We exclude the latter on the basis of the gradual development of the failure and the absence of a systolic blowing murmur.

These assumptions proved to be correct, as we found in the necropsy a right ventricular stenosis with dilatation of pulmonary conus and right atrium, along with liver enlargement and lungs free of congestion.

This is the anatomic picture of Bernheim's syndrome and furnishes further proof for the statements made by Atlas and associates,[4] Russek and Zohman,[3] and Fishberg[8] about the existence of this clinical syndrome and the possibility of this diagnosis during life.

Furthermore, this case points out another possible origin of the syndrome: the infarction of the interventricular septum.

SUMMARY

True Bernheim's syndrome is an hypertrophy of the left ventricle with a bulging septum protruding into the right chamber and therefore preventing its normal filling.

The same right ventricular stenosis may result from a septal infarction. Both situations lead to a clinical picture allowing the diagnosis during life.

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ACUTE ISOLATED MYOCARDITIS SIMULATING CORONARY OCCLUSION

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ACUTE isolated myocarditis is a disease in which the myocardium alone is the seat of inflammatory changes, the endocardium, pericardium, and heart valves being unaffected. Furthermore, in this condition, there exist no complications by known systemic infections or other kinds of heart disease. The lesions in the fatal type are more or less of a diffuse nature.

The first clear account of this disease was given by Fiedler[1] in 1890, and hence it is often referred to as Fiedler's myocarditis. Although there have been many subsequent reports of this condition, Saphir[2] has pointed out that the clinical picture is invariably one of rapidly progressive myocardial failure or sudden death. The case to be presented is unusual in that the clinical picture and electrocardiographic findings resembled those of coronary occlusion, the correct diagnosis being made only on post-mortem examination.

CASE REPORT

The patient was a 44-year-old white man, who was admitted to the hospital on June 16, 1952. He had felt well until three days prior to admission when he noted some chilliness and fatigability in the evening. The following afternoon he developed a steady aching pain with intermittent sharp, jabbing pains, situated along the left border of the sternum and over the left side of the chest. This pain was associated with an aching in the left arm, especially in the region of the elbow and wrist. The pain came on while at rest and subsided spontaneously in two to three hours. The next afternoon this pain recurred and gradually mounted in intensity until the morning of admission to the hospital. At this time he received Dilaudid (1/3 grain) subcutaneously with subsequent relief of pain, and there was no further recurrence up to the time of death.

Prior to this illness, the patient had felt well. There was no history of dyspnea or chest pain on exertion and no history of antecedent cold, sore throat, or upper respiratory infection. Except for double pneumonia and typhoid fever in childhood, he had had no significant illnesses in the past. There was no family history of heart disease.

Physical Examination.—This revealed a middle-aged white man of ashen color, perspiring profusely, and with cool extremities. Temperature was 99.6 degrees, pulse, 110 per minute, respirations, 20 per minute. He was able to be flat without dyspnea. The fundi were normal. The neck veins were not distended. The lungs were clear with no râles being heard. The heart appeared to be of normal size on percussion and the rate was regular. Marked variation in the intensity of the heart sounds was present intermittently; no murmurs were heard. Blood pressure was 96/64 mm. Hg with marked pulsus alternans. The liver was not palpable. No peripheral edema was present.

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Clinical Course.—Shortly after admission the patient was placed in an oxygen tent and was given 400 mg. Depoheparin intramuscularly, 300 mg. Dicumarol by mouth, and 2 grains of Luminal Sodium subcutaneously. He appeared to improve markedly after a short time in the oxygen tent. The profuse perspiration ceased, his pulse rate fell to 72 per minute and was of fairly good quality, and the blood pressure increased to 104/84 mm. Hg, the pulsus alternans no longer being present. Twenty hours after admission the blood pressure dropped to zero rather suddenly, repeated small emeses occurred, and in two hours the patient was dead.

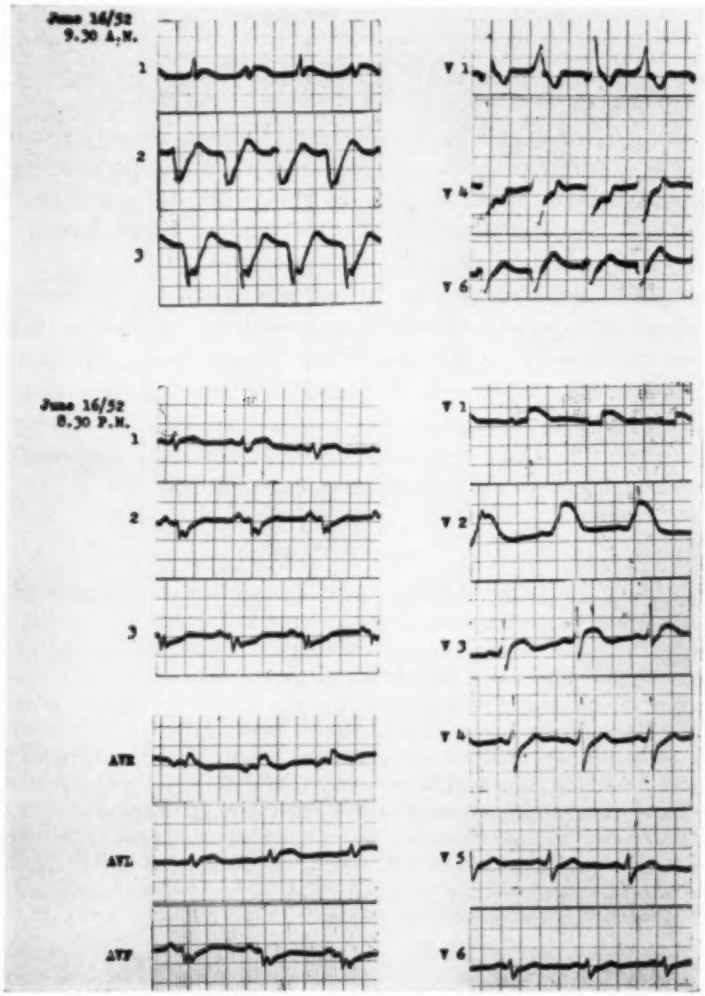

Fig. 1.—For description see text.

Laboratory Data.—The day of admission the hemoglobin was 14 grams, white blood cells 11,650 with 42 per cent lymphocytes. The sedimentation rate was 11 mm. in one hour (Westergren Method). Blood Kahn was negative. Urinalysis was negative. Prothrombin activity was 55 per cent of normal the day of admission, and 39 per cent the next day. An electrocardiogram taken early on the morning of admission (9:30 A.M., Fig. 1) showed a supraventricular tachycardia, rate 110, which was felt to be a nodal rhythm, atypical right bundle branch block pattern (QRS 0.16) with electrical alternation, the presence of a Q wave in every other beat in Leads V_1 and V_6,

S-T segment elevation in Lead I, and depression in V_4. A second electrocardiogram done in the evening (8:30 P.M., Fig. 1) showed a regular sinus rhythm, rate 80. The bundle branch block was still present while the electrical alternation had disappeared, but in the limb leads there was alternation in the width of the QRS interval. Slight S-T elevation was seen in Leads I and aV_L and marked S-T elevation in V_1 to V_3 with S-T segment depression in V_4 to V_6. It was felt that the electrocardiographic tracings were consistent with recent myocardial infarction involving the interventricular septum.

Autopsy Findings.—Post-mortem examination was performed five hours after death. The body was that of a 44-year-old white man of good nutrition and normal development. Cyanosis and peripheral edema were not present. There was no lymphadenopathy.

The pleural cavity contained a minimal amount of fluid. Except for mild congestion, the lungs appeared normal. The heart weighed 480 grams, the enlargement being diffuse. The myocardium was slightly softer than normal though not flabby. Scattered diffusely throughout the myocardium were whitish patches measuring from 0.5 to 1.5 cm. in diameter. These extended from the subendocardial region into the myocardium but did not appear to involve the endocardium or pericardium. The muscle fibers pulled apart with more ease than normal, both in the whitish patches and elsewhere. The patchy distribution of the lesion appeared most prominent in the left ventricle and involved the anterior, posterior walls and interventricular septum indiscriminately. The endocardium and pericardium of both ventricles and auricles appeared normal.

The coronary arteries showed only a minimal degree of arteriosclerosis. Except for mild congestion in the liver the remainder of the organs appeared normal.

Fig. 2.—Section of myocardium of left ventricle (×110).

Microscopic Examination.—Multiple blocks were examined from both the right and left ventricular myocardium. The striking pathology consisted of a diffuse and heavy cellular exudate which separated the muscle fibers. This change was diffuse and involved both the left and right ventricles (Figs. 2 and 3), only small patches escaping. The reaction appeared to be most intense toward the endocardial half of the muscle. The cellular exudate consisted almost entirely of lymphocytes and monocytes with an occasional eosinophil. The muscle fibers showed patchy necrosis, evidenced by loss of striations in some areas with deep pyknotic and irregular nuclei and the presence of blobs of eosinophilic staining material within fibers which gave them a smudged appearance. In many areas there was marked fragmentation of the fibers. There was no increase

in interstititial fibrous tissue and the blood vessels appeared quite normal. No pericarditis was noted. The only significant findings in the lungs were a few small focal collections of hemosiderin containing phagocytes. Lymph nodes (mesentery) were quite normal; there was no suggestion of leukemia. Bone marrow showed normal cellularity; there was no suggestion of a leukemic involvement. The liver, spleen, adrenals, thyroid, and kidneys showed no significant lesions other than an acute venous congestion.

Fig. 3.—Section of myocardium of right ventricle (×110).

DISCUSSION

In the cases that Fiedler described of "acute interstitial myocarditis," the clinical picture was one of rapidly progressive myocardial failure. Scott and Saphir[3] in one of the first clinical reports of this condition in the English literature also pointed out that the course taken by these patients was that of progressive heart failure unassociated with any of the known factors leading to such failure. Subsequently, many reports have appeared of sudden death,[4,5,6] in which the only lesion present at post-mortem examination to account for this was an acute myocarditis. Luongo[6] has recently emphasized the importance of a careful microscopic examination of the heart in persons who die unexpectedly for no readily apparent cause on routine examination.

In the case reported here, the outstanding feature was the severe sternal and left chest pain. This resembled the pain of coronary occlusion in that it gradually increased in intensity over a period of 15 hours until relieved by Dilaudid, and it was accompanied by pain in the left arm. Furthermore, the clinical picture was one of shock with no evidence of heart failure, and the electrocardiographic picture was consistent with a coronary occlusion. There was only slight elevation of temperature, slight leukocytosis, and a normal sedimentation rate.

In retrospect, there would appear to be two features in this case that might suggest the correct diagnosis. The first was the occurrence of a chilliness at the onset of the illness prior to the beginning of the chest pain. Hansmann and Schenken[8] have indicated that rapidly developing myocarditis is likely to be signalized by a chill. This is not a usual feature of coronary occlusion. The second unusual feature in this case was the presence of an increase in the total number of lymphocytes in the blood. Altschul[9,10] has pointed out that in myocardial infarction a marked decrease in the absolute lymphocyte count often occurs. The normal lymphocyte count is usually given as 2,000 to 3,000 per cubic millimeter and the highest figure given by some authors, as the upper limit of normal is 4,000. In this case, the lymphocyte count was 4,893. Although such an increase, in itself, by no means occurs only in myocarditis, it may serve as a warning for other etiologic possibilities in a person suspected of having a coronary occlusion.

SUMMARY

A case of a middle-aged adult has been presented whose clinical course and electrocardiographic findings were those of coronary occlusion. At post-mortem examination an acute myocarditis was found with no significant lesion in other organs of the body. Since there is strong evidence that these cases may be of viral etiology, their future recognition becomes of greater importance as more potent antibiotics become available.

Thanks are due to Dr. Maurice Fox for permission to report this case and to Dr. H. E. Taylor for assistance in presentation of the pathological material.

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Critique

THE THEORETICAL AND EXPERIMENTAL BASES OF THE FRONTAL PLANE VENTRICULAR GRADIENT AND ITS SPATIAL COUNTERPART

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INTRODUCTION

IN 1934 Wilson and associates[1] did a series of experiments on the dog's heart to determine whether, as predicted by simple theory, the time integral of the electrocardiographic potential was zero for varying heart conduction paths. They found the hypothesis untenable even to the first order but discovered that there was a substantial correlation between the area of the QRS complex and the T area and that this relationship was relatively unaffected by the conduction path through the heart even though the axis and the action potential form and magnitude varied considerably.

In effect, they observed that the algebraic sum of the manifest QRS and T versus time areas approximated a constant value for various conduction paths and that this summation residue had certain vectorial properties which made it of special interest. They called the residue ventricular gradient and considered it a quantity worthy of theoretical and empirical investigation. It should be noted, however, that the ventricular gradient is not predicted by simple theory but is instead a partially understood deviation from simple theory. It should also be noted that in a strict mathematical sense the ventricular gradient is not truly a gradient.

Subsequent to Wilson's pioneering, the notion of the ventricular gradient was taken up by the schools of Ashman and associates,[2-5] Schaefer[6] and others and has been used often on an empirical basis until it has now become a part of the regular electrocardiographic vocabulary. It is seldom realized, however, that the ventricular gradient concept is on an insecure theoretical foundation and must at present derive its justification for existence purely from empirically discovered usefulness in description of electrocardiographic results or in empirical correlation with other methods of heart diagnosis.

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It is the purpose of this paper (1) to re-examine some of the experimental and theoretical bases of the ventricular gradient (V G) concept in order to determine whether an objectively justifiable significance can be found for it, (2) to examine the logical extension of the ventricular gradient concept to three dimensions, and (3) to provide some new experimental data to fill gaps in this appraisal.

I. THEORETICAL CONSIDERATIONS

If the ventricular gradient is to be traced back theoretically to the electrophysiologic events which accompany the heartbeat, it is necessary to re-examine carefully all of the rough approximations which led Wilson originally to expect the ventricular gradient to be identically zero, or nearly so, and to determine which one or ones of the postulates are faulty and thus major contributors to the ventricular gradient. For this ventricular gradient does exist, and there are some heart strip measurements[7] which are interpreted to mean that the T and QRS may be intrinsically concordant. We may thus be led at best to identify the ventricular gradient with certain specific physiologic factors or, at worst, to discover which factors must be more exactly studied.

We can start with a fairly safe assumption that the electrical current superposition theorem applies to the ventricular gradient measurement with good accuracy. According to this theorem we can expect linear addition of measured action potential components in terms of their single fiber dipole sources. Thus, if a particular fiber group a contributes a time dependent current $i_a = f_a(t)$, we can confidently expect that at any electrode pair position P there will be a potential difference $e_{ap} = Z_{ap}\, i_a$ irrespective of any other potentials produced between the same electrodes as a result of other curents from other fibers. Z_{ap} here plays the role of a transfer impedance and reflects the geometry and distance from heart to the leads as well as body conductivity but is a constant for any one situation. The whole measured electrocardiographic potential at electrodes P can be specified as $E_p = \sum_a Z_{ap}\, i_a$ and can be thought of simply as the algebraic sum of all the local action potentials resulting from action currents produced by individual muscle fibers, each corrected for its position and orientation with respect to the leads. It will prove convenient to think of the individual i_a currents as made up of equal and opposite paired currents which, pair by pair, constitute current dipole moments when multiplied by their physical separation.

The superposition theorem is open to minor objections on the basis of polarization nonlinearity in tissues and depends slightly upon frequency effects but is almost certainly accurate for all physiologic purposes. There is, however, an important related factor which has had little attention in the literature, even in such careful treatments as that of Schaefer.[6] The superposition theorem applies in terms of currents, not in terms of the potential sources producing the currents. If, for example, two parallel adjacent fiber groups each produce one microampere-millimeter of current dipole moment and each, excited alone, produces one microvolt of measured action potential at a remote point, the two fiber groups stimulated simultaneously will produce substantially less than two microvolts, but more than one, at the measuring place. The explanation lies in the fact that each reduces the electromotive force in the other's circuit so that each supplies less than unit current and hence through the superposition theorem, less than unit-measured action potential.

We can estimate the magnitude of this effect roughly by noting that measured electrocardiograms of 2 to 3 mv. are common, especially in precordial leads while the known electromotive force behind the action current process is of the order of 100 millivolts. Reasoning from dipole theory that the extracellular potential differences within the heart giving rise to these remote electrocardiograms must be at least 10 to 20 mv. to allow for measured attenuation, we conclude that this factor may be important in originating the ventricular gradient. The T-wave changes occur much more slowly than the QRS changes and consequently for equal time-potential-area involve smaller local currents spread over a longer time. Thus, they are less subject to this interaction effect. As this analysis does not take into account series addition of fibers, it cannot be used easily to make accurate determinations, yet its indications are qualitatively pertinent.

In this connection it is also important to notice that tissue impedance is markedly sensitive to polarizing currents and that consequently the action current from one fiber is likely to change appreciably the resting current from another and thus cause a "resting" cell to contribute a current component which is not compensated between QRS and T as is the ideal normal action potential. This "passive" effect can of course occur also during normal active phases of contraction.

A second group of phenomena which contribute to the ventricular gradient deviation from zero have to do with the change of geometry in and about the heart during contraction. To illustrate this point with an extreme case, think of a fiber which, between the QRS and T phases of its own activity, might conceivably be turned end for end as a final result of ventricular contraction. This fiber would yield a completely concordant QRS and T, even though fundamentally the fiber was producing normal discordant currents. It is not implied that such complete reversal actually occurs but it must be obvious that even a small angular shift across the median plane can cause reversed representation of a fiber since a cosine law applies. In addition to rotational changes, the heart contraction is a gross enough phenomenon that spatial translation shifts the magnitude of recorded potential in terms of distance to electrodes even without reorientation. Whether the spatial shift or the angular reorientation effect dominates is an open question worthy of further study.

The effects thus far discussed could make a spurious "gradient" appear where the contributing fibers are themselves perfectly discordant in QRS and T-time areas. Some final considerations have to do with components of the ventricular grxdient, resulting from phenomena intrinsic in individual fibers, in contrast to the previous extrinsic causes.

We are all familiar with the action potentials produced by isolated nerve or muscle fibers and the classical transition between diphasic and monophasic forms as the fiber is injured in the interelectrode region. It is possible within bounds to make a quantitative analysis of the comparable events in the heart syncytium and to associate the measured ventricular gradient with specific nonuniform fiber properties. In this theoretical treatment certain powerful simplifying assumptions regarding the muscle action currents which ultimately give rise to the measured electrocardiographic potentials can be made with some safety.

1. Any straight uniform circular region of an individual heart muscle fiber can contribute to the total heart dipole current only along the direction of the fiber. This implies that the fiber surface is uniform circumferentially.

2. The contribution to externally measured potential difference due to any fiber section less than one cm. long can be accurately represented by an ideal dipole source located at the mean fiber position.

3. The superposition theorems of classical electrical theory can be applied to the heart if cognizance of impedance nonlinearity is taken and due allowance is made for varying relative source-sink impedance ratio as addition between fibers occurs.

4. The time sequence of potential changes in each normal fiber region follows a similar course subject to minor local variations.

Let us rederive in a simplified but more generalized fashion the mathematical relationships which led Wilson to suspect that ideally there should be no ventricular gradient as measured from external leads. Then let us examine the approximations in this theory to determine which of them represent Wilson's "local variations" which lead to the experimentally observed ventricular gradient.

Ideally the action potential may be regarded as a traveling wave of the form

$$V_{x,t} = \phi(x-ut) \qquad (1)$$

where ϕ is a functionally constant wave form, x is a positional coordinate along the fiber, u is the conduction velocity, t is time and $V_{x,t}$ is the transmembrane potential at position x at time t.

If, as an approximation already discussed, we regard the internal fiber resistance as large compared with the total external saline shunt, the local action current is determined solely by the longitudinal myoplasmic resistivity ρ_1, so that the longitudinal local current I_1 is $\frac{\partial \phi}{\partial x}\frac{1}{\rho_1}$, i.e., the fiber current at any chosen position and time is proportional to the longitudinal potential gradient.

By differentiating the Equation (1) partially

$$\frac{\partial V_{x,t}}{\partial t} = -u\ \phi'\ (x-ut)$$

$$\frac{\partial V_{x,t}}{\partial x} = \phi'\ (x-ut)$$

$$\frac{\partial V_{x,t}}{\partial t} = -u\ \frac{\partial V_{x,t}}{\partial x}$$

whence

$$I_1 = \frac{-1}{\rho_1 u}\ \frac{\partial \phi}{\partial t}.$$

That is, a short region of muscle fiber contributes to the total action current a dipole current component directed along the length of the fiber and proportional to the time rate of change of the transmembrane potential, and inversely proportional to the myoplasmic resistivity and to the velocity of conduction. Due care must, of course, be taken to observe conventions of sign. During the early excitatory phases the external current will flow in such a direction as to make the region ahead of the impulse more positive in potential while in the main recovery phase the current flow will be reversed.

The total potential difference at any external set of leads must be equal to some set of constant transfer impedances Z_a times the current dipole strengths.

$$E_{\text{external}} = \sum_{\text{fibers}} Z_a I_{1a} = \sum \frac{-1}{\rho_{1e}\, u_a} Z_a$$

but we can identify this function E_{external} as being closely related to the ventricular gradient by the equation

$$\text{ventricular gradient (VG)} = \int_{\text{cycle}} E_{\text{external}}\, dt$$

where this is one component equation and is repeated for each of the vector components under consideration and the integration is performed over exactly one entire heart cycle. The component ventricular gradient then becomes

$$VG = \sum \frac{-Z_a}{\rho_{1a} u_a} \int \frac{\partial \phi_a}{\partial t}\, dt = \sum \frac{-Z}{\rho_{1a} u_a} [\phi]_{\text{cycle}}$$

If the heart fiber is to return to exactly the same state after completing a cycle, ϕ has the same value before and after the cycle and consequently $[\phi]$ has a value of zero. This being true for each fiber individually, it obviously is applicable to the whole integrated pattern.

A time integral voltage area residue measured at any point on the body can thus exist intrinsically only if (a) the wave form changes along individual fibers, (b) the impulse velocity μ changes, (c) the fiber tapers, i.e., the resistivity ρ changes.

The most radical possible kind of wave form change is abrupt cessation of the wave train, and this can give rise to the "injury current" monophasicity associated with drastic recent trauma.

If the impulse velocity shifts without concurrent wave form changes, a residue accumulates in the integrated external dipole current. This effect has been associated with the experiments using local cooling although temperature change also influences the other factors secondarily.

Taper of the fibers introduces a varying area of active membrane and a changing impulse velocity so that it could be responsible for much of the normally measured gradient in the absence of injury. It is interesting to point out that maximal gradient effect can be expected for a given mass of muscle when the (Rushton) analytical unit of length approaches the fiber length. This length for heart muscle must be of the order of a millimeter[8] and consequently nearly optimal for the fiber length found in the heart.

Generalizing, then, we might say that at least four factors present in the normal heart can and probably do contribute significantly to production of the ventricular gradient. As the normal or "ideal" components of action current integrate to zero over a cycle, the ventricular gradient might be expected to emphasize factors which alter (1) the heart's geometry (hypertrophy, etc.) and mechanical cycle, (2) its time sequence of events (through upset of impedance relationships), (3) its fiber terminations, velocity of conduction, and metabolic physiology (impaired circulation, etc.), and (4) its injury currents (incipient infarction).

While these factors can perhaps be separated experimentally and examined individually, this has not yet been done adequately and consequently cannot be used in evaluation of clinical results.

II. THE EXPERIMENTAL BASIS

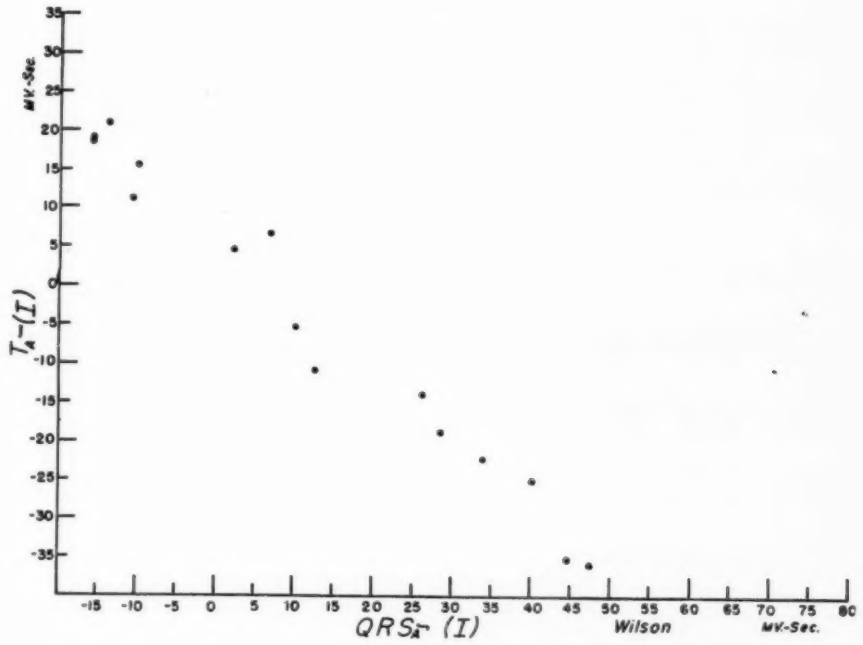
1. *Analysis of Wilson's Experiment.*—Wilson and associates[1] stimulated a dog's heart from fifteen different points and found the ventricular gradient reasonably constant in spite of the greatly different pathways of excitation and grossly different patterns and electrical axes. This fundamental experiment is actually the basis for the whole ventricular gradient concept but was never repeated. We calculated in Wilson's data the standard deviation of the magnitude of the ventricular gradient; it was about ± 25 per cent of the mean. This he considered a small variability.

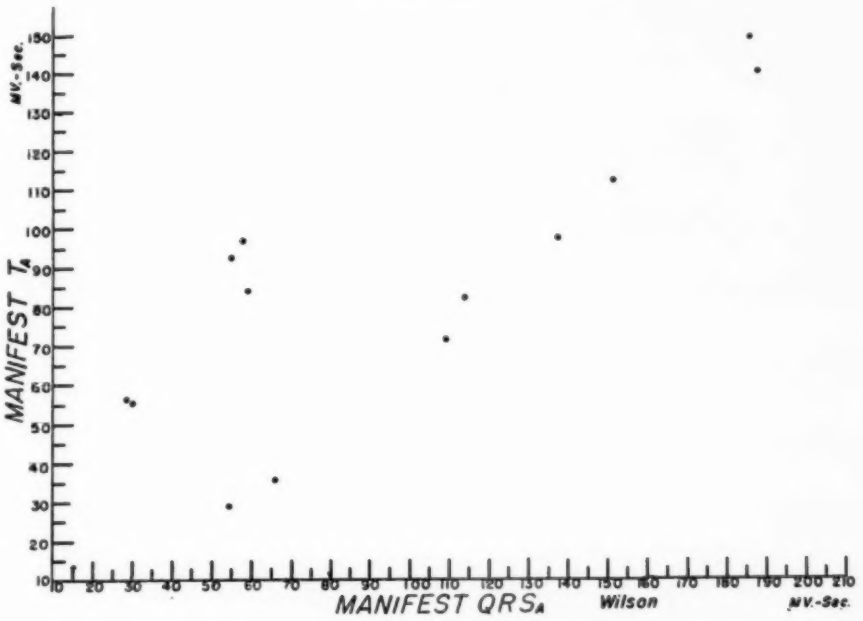
Wilson tried to explain the variability as due to the technical error of measurement, but his measurements were made with great care. That the variability of the ventricular gradient cannot be due mainly to the technical error of measurement is shown by plotting from Wilson's data the T area (T_A) versus the QRS area (QRS_A) for Lead I (Fig. 1, *A*). The correlation is nearly perfect, with a correlation coefficient of $r = 0.987$. Such correlation would be impossible in the presence of a large source of measurement error. Figure 1, *B* shows a plot of the manifest T area versus the manifest QRS area from the same experiment. The correlation still is high ($r = 0.88$), but it is poorer than that for Lead I.

There is still one important point to be made regarding Wilson's experiment. One of the main problems in the relationship between QRS and T is their concordant direction. In Wilson's experiment, however, the direction of QRS and T was discordant. The applicability of Wilson's experiment to the normal ventricular gradient in man, therefore, is limited.

2. *Variation of the Pathway of Ventricular Activation in Man.*—The first electrocardiogram of one patient with arterial hypertension and coronary artery disease (woman, 76 years) treated in the hospital for 3 weeks with bed rest, showed right bundle branch block (with M-shaped QRS contour in V_1 and V_2), and 2:1 atrioventricular block (Fig. 2:4/17). One day later, (4/18), the atrioventricular block became complete with a left idioventricular pacemaker. On April 24, complete atrioventricular block was still present, but the idioventricular pacemaker had shifted from left to right. This, therefore, constitutes the human counterpart of Wilson's experiment with spontaneous changes of the ventricular pathway of excitation instead of variation of stimulating electrode placement.

A.





B.

Fig. 1.—*A.* QRS area (QRS_A) versus T area (T_A) in Lead I, from Wilson[1] and associates' experiment on a dog, with electrical stimulation of the ventricles from 15 different points. The correlation is nearly perfect.

B. Manifest QRS versus manifest T area, from Wilson[1] and associates' experiment. The correlation is still strong, but not as good as in Lead I.

There is, of course, in this case the possibility of changed myocardial condition in addition to the change of the ventricular pathway. However, there was nothing in the clinical condition to suggest such a change. The patient was slowly improving from April 17 to 24. We used Wilson's method for the measurement of areas; a slide was made of Fig. 2, and the areas were measured with a planimeter on the projection screen. The results are shown in Table I. The variations of the ventricular gradient (VG) are in the order of Wilson's experiment.

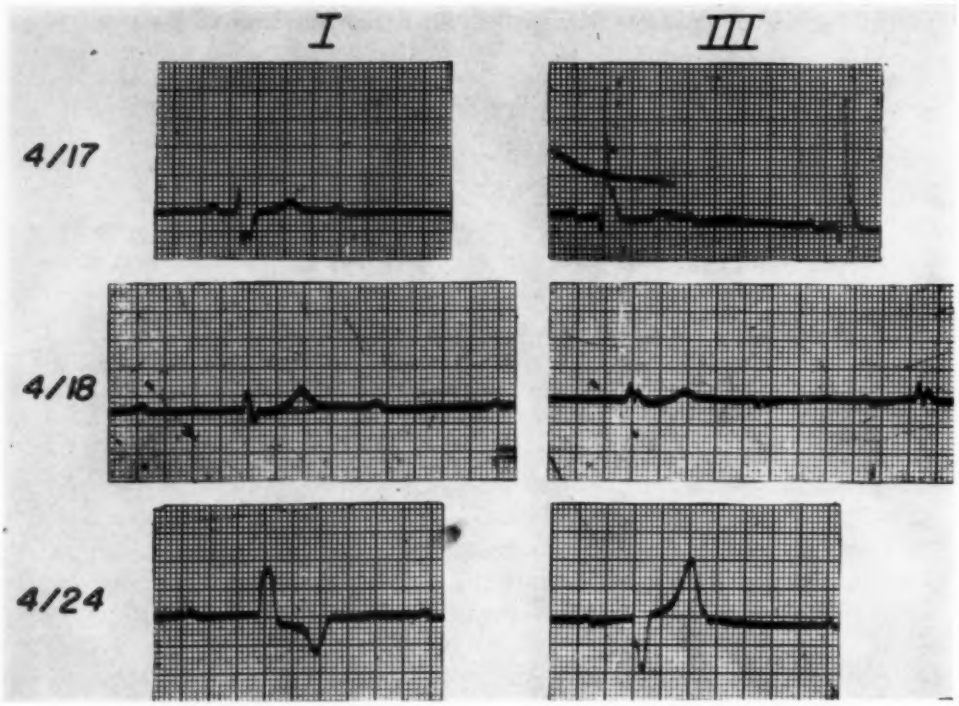


Fig. 2.—Changing ventricular pathway in a patient. 4/17, Right bundle branch block, 2:1 atrioventricular block; 4/18, Complete atrioventricular block, left idioventricular pacemaker; 4/24, Complete atrioventricular block, right idioventricular pacemaker.

TABLE I. CHANGES OF THE AREAS OF QRS, T, QRS-T AND OF THE VENTRICULAR GRADIENT (VG) WITH VARIATION OF VENTRICULAR PATHWAY OF ACTIVATION IN ONE PATIENT

DATE	LEAD	QRS AREA	T AREA	QRS-T AREA	VG
4/17	I	−11.04	+ 4.00	− 7.04	29.4
	III	+24.64	+ 3.84	+28.48	
4/18	I	+ 1.36	+12.24	+13.60	24.4
	III	+ 3.20	+ 6.80	+10.00	
4/24	I	+18.72	−15.20	+ 3.52	27.6
	III	−15.20	+37.36	+22.16	

3. *Normal Standards.*—We have calculated from the means and standard deviations the range limits of the magnitude of the ventricular gradient for 98 per cent of the normal population for our group of 107 men and for Ashman and Byer's[3] group of 213 normal subjects with heart rates between 40 and 99 from their Fig. 3, and have added also Byer[9] and associates' values for 80 men and 84 women (Table II). The values of these different groups agree quite well and seem to be fairly representative of American adult population. Without correction for the heart rate, the normal limits extend from 0.0 to 25.0. According to Welsch[10] the upper limits extend even to 30 units. Whether these normal range limits are wide or narrow can best be tested by comparison with cardiac patients.

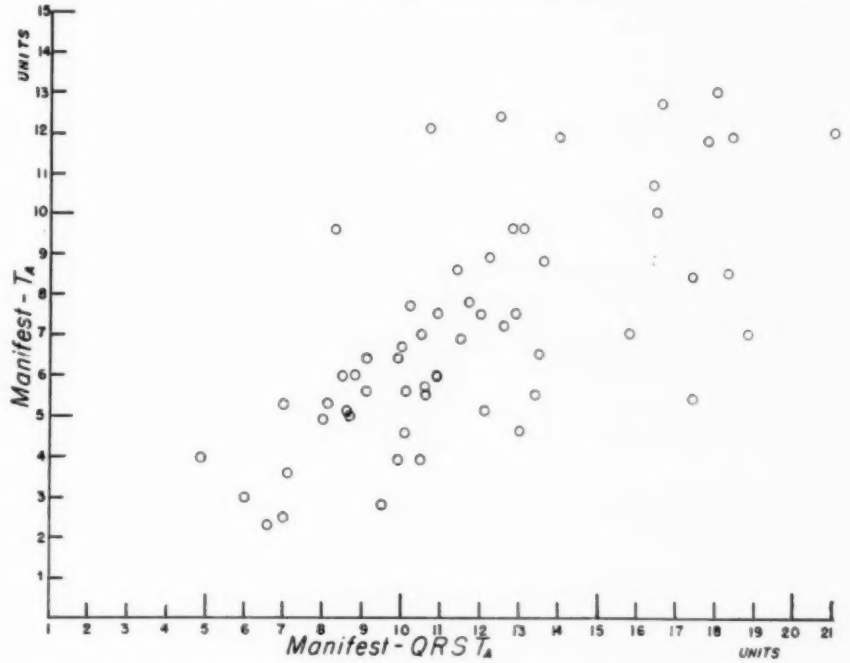


Fig 3.—Manifest QRS-T area (abscissa) versus manifest T area (ordinate). Ashman unit = 4 microvolt seconds. Correlation is about the same as in Ashman and Byer's[3] Fig. 3.

TABLE II. MEANS, STANDARD DEVIATIONS, AND RANGE LIMITS FOR 98 PER CENT OF NORMAL POPULATION

GROUP	HEART RATE	N	MEAN	S. D.	98% LIMITS	
					L	H
Ashman (1943)	40–59	33	16.72	4.64	5.44	28.00
	60–79	101	13.14	4.49	2.23	24.05
	80–99	79	11.33	3.91	2.83	20.83
Total	40–99	213	13.24	4.66	1.92	24.56
Beyer et al. (1947)	—	80m	11.77	4.52	0.79	21.75
	—	84f	11.34	3.67	2.42	20.26
Our Group	50–90	107m	11.33	4.71	−0.08	22.78

L = low, H = high.
m = male, f = female.

We selected for this purpose three studies by American, German, and French authors, which, on the background of a larger literature, are fairly representative for the general situation.

Pantridge[11] found an increasing incidence of abnormally small ventricular gradients with the degree of myocardial involvement in twenty-three patients with left bundle branch block. However, none of the seven cases with "abnormally" small ventricular gradient exceeds the normal limits as shown in Table I.

In Schaefer's[6] material of forty cardiac patients with various types of pathology, the upper normal limit was slightly exceeded only in one patient with left ventricular enlargement and a history of paroxysmal tachycardia attacks (see Schaefer,[6] Fig. 196). The only abnormality in the electrocardiogram was S-T depression in Leads II and III and a diphasic T_2. On the other hand, in many patients with very advanced myocardial involvement, the ventricular gradient was "normal."

In Papanicoli's and Vlachoyanni's[12] fifty cases with myocardial infarction the ventricular gradient was within the normal limits in all patients, although the mean of the group of patients was significantly lower than the normal mean.

This may suffice to show that the range limits of the normal ventricular gradient are exceedingly wide. Patients even with very advanced myocardial involvement fall inside these range limits with very few exceptions.

We are aware that the direction of the ventricular gradient and its components may be abnormal even when the magnitude is normal, but in most cases with abnormal area axes the mean QRS or T amplitude axes are also abnormal, so that the area axes give little additional information. Some material pertinent to this question is presented in Section IV.

4. *Correlation Between QRS Area and T Area in the Frontal Plane.*—Since the ventricular gradient concept implies a numerical relationship between QRS area and T area, its definition stands or falls with the presence or absence of such relationship. It is surprising that no such study has been reported.

Ashman and Byer[3] plotted in their Fig. 3 the magnitude of manifest QRS area versus the manifest QRS-T area (gradient); although no statistical analysis was made, a definite correlation is obvious. As the abscissa represents a prominent component of the ordinate one would expect some correlation to be found. For demonstration, we have plotted in sixty normal subjects the manifest T area (instead of the manifest QRS area in Ashman and Byer's Fig. 3) versus the manifest QRS-T area. The correlation in our Fig. 3 is very similar to that of Ashman and Byer's diagram but does not necessarily imply a fundamentally important relationship.

In order to establish whether the manifest QRS-T area was fundamentally more internally consistent than the individual lead components, we investigated the correlation between QRS area and T area for Lead I as well as for the manifest areas in three groups of normal subjects, selected from different points of views:

Group 1 consisted of sixty normal middle-aged men, subdivided in three groups of twenty with (a) semivertical or vertical, (b) intermediate, and (c) horizontal or semihorizontal electrical heart position but all within a range of the heart rate not exceeding 20 beats.

Group 2 consisted of fifty-eight normal middle-aged men with an angle of dA° between the mean spatial QRS and T vector between 45° to 65°. In a previous investigation[13], a significant correlation between the magnitude of the mean spatial QRS and T vectors was found for this range of dA°. Therefore, this group was preselected to show a correlation between QRS and T areas.

Both Groups 1 and 2 were part of a larger group which has been under observation for five years. On the testing day (in annual intervals) they were submitted to a thorough examination including routine clinical methods, history, and numerous laboratory tests including tolerance to various physiologic stresses. Therefore, any diseased condition can be excluded with a greater degree of probability than is the case in most normal control groups. This is important for our problem, because the possibility of primary T changes should be eliminated as far as possible. There was some slight overlapping between Groups 1 and 2 in that six subjects were members of both groups. The areas were mechanically measured with the aid of a magnifying glass and expressed in Ashman units (Unit = 4 microvolt seconds).

Group 3 consisted of forty-nine young men from 25 to 35 years who were found to be normal in a thorough clinical examination but were not submitted to the numerous laboratory tests of Group 1 and 2. The areas were measured with an especially developed electronic integrator.

The principle of electrical area measurement is not new; it is generally conceded that such methods are more accurate than mechanical area measurement. Johnston and associates[14] applied such a method to the measurement of QRS and T areas, but our method, described in Appendix II, is fundamentally similar but has certain technical advantages. The over-all accuracy of electronic area measurement, expressed as coefficient of consistency,[15] was very high (0.96 for QRS area and 0.95 for QRS-T area).

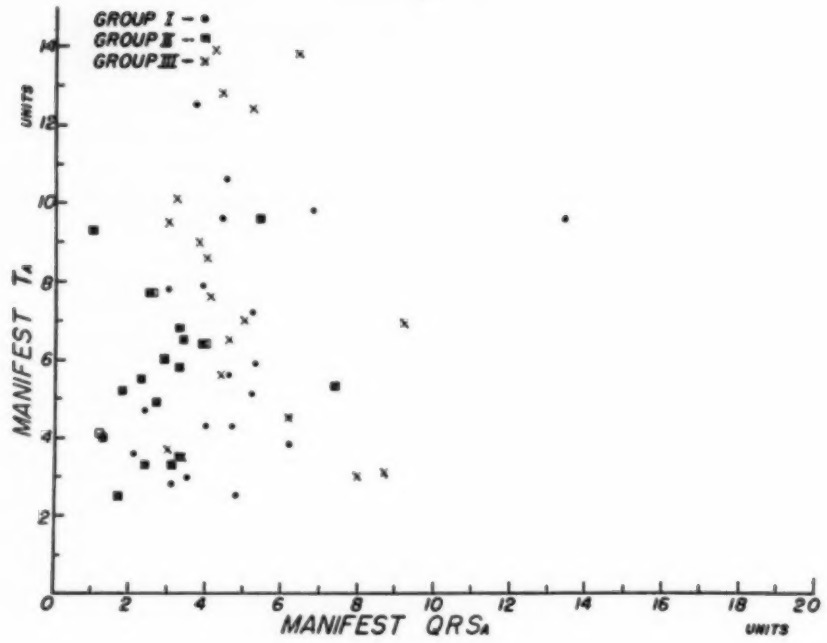
Table III summarizes the results, which were practically identical in all three groups. No correlation was present between the manifest QRS and T

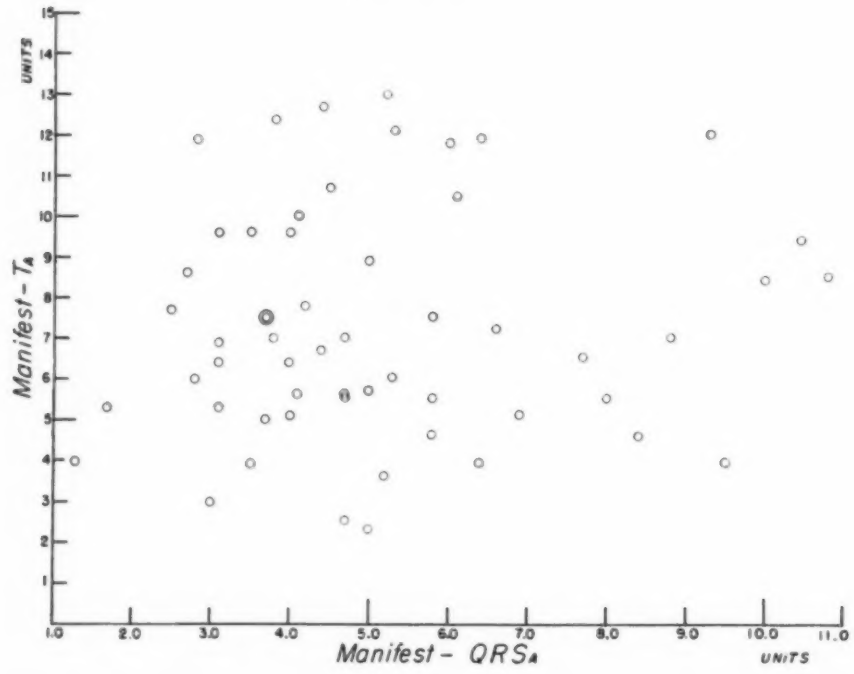
TABLE III. CORRELATION COEFFICIENT (r) BETWEEN QRS AND T AREA

GROUP	N	MANIFEST		LEAD I	
		r	p	r	p
A	60	0.087	>0.2	0.388	0.01
B	58	−0.021	>0.2	0.175	0.20
C	49	0.062	>0.2	0.445	0.01

p = level of statistical significance, N = number of men.

A.





B.

Fig. 4.—Manifest QRS area (abscissa) versus manifest T area (ordinate).

A. Group of sixty normal men; dots: horizontal and semihorizontal electrical heart position; squares: intermediate electrical heart position; x = vertical and semivertical heart position. Absence of correlation in all positional groups.

B. Group of fifty-nine normal men with angle between spatial mean QRS and T amplitudes from 45° to 65°. Absence of correlation.

areas; the correlation coefficient was close to zero. The absence of correlation in Groups 1 and 2, therefore, is not due to the technical error or mechanical area measurement. Figures 4, *A*, *B*, and *C* show the manifest QRS area plotted versus the manifest T area for the three groups. Within the large area of normal scatter, no prediction of the T area from the QRS area is possible, and consequently the ventricular gradient seems to be meaningless in view of normal variations.

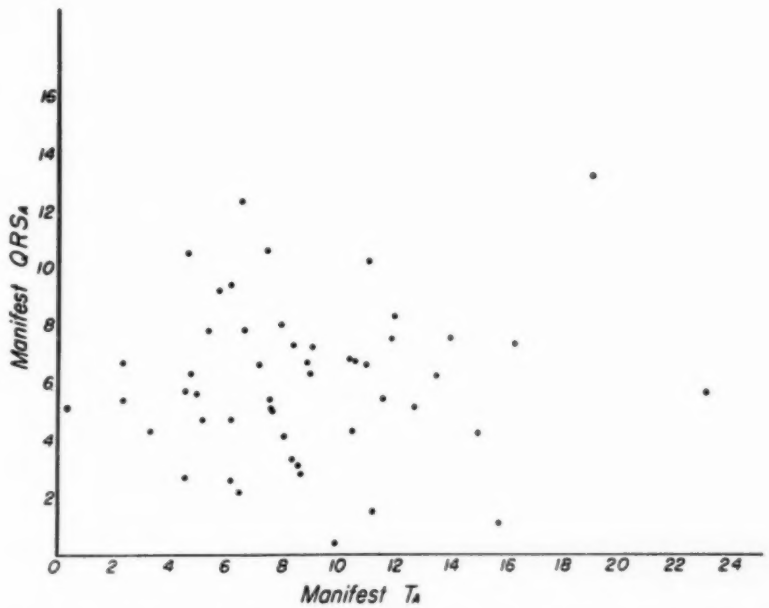


Fig. 4C.—Manifest QRS area (ordinate) versus manifest T area (abscissa). Group of fifty normal men: electronic area integration. Absence of correlation.

In contrast, there was a statistically significant positive correlation between the QRS and T areas for Lead I in Group 1 (shown in Fig. 5) and Group 3. In Group 2 the correlation coefficient for Lead I was higher than that for the manifest areas but did not attain statistical significance. There is no effect of electrical heart position on the presence of correlation in Lead I or absence of correlation in the manifest areas (Fig. 4, *A*). This situation is discussed in Section III.

There was a significant positive correlation between the elevation angle α of the manifest QRS and T area in Groups 1 and 2, ($r = 0.498$ and 0.370) which should be expected because of the known correlation between the mean QRS and the mean T amplitude axes. The absence of a significant correlation in Group 3 may be due to the exaggeration of slight S-T deviations with the electronic area measurement.

III. THE SPATIAL VENTRICULAR GRADIENT

1. *Analysis of Existing Literature.*—Wilson and associates[1] as well as Ashman and Byer[4] were aware that the frontal plane ventricular gradient must have some spatial correlate. In their earlier work, Ashman and Byer studied the relationship between the anatomical axis H, the QRS_A axis, and the gradient axis (VG) in different positions as projected on the frontal plane. Without question a different spatial orientation will project differently, and it is to Ashman and Byer's credit that they were able to demonstrate this in a semiquantitative way. This, however, is not a suitable method for measurement for various reasons, and actually no values of a spatial ventricular gradient in terms of spatial direction (azimuth, elevation) or magnitude were given.

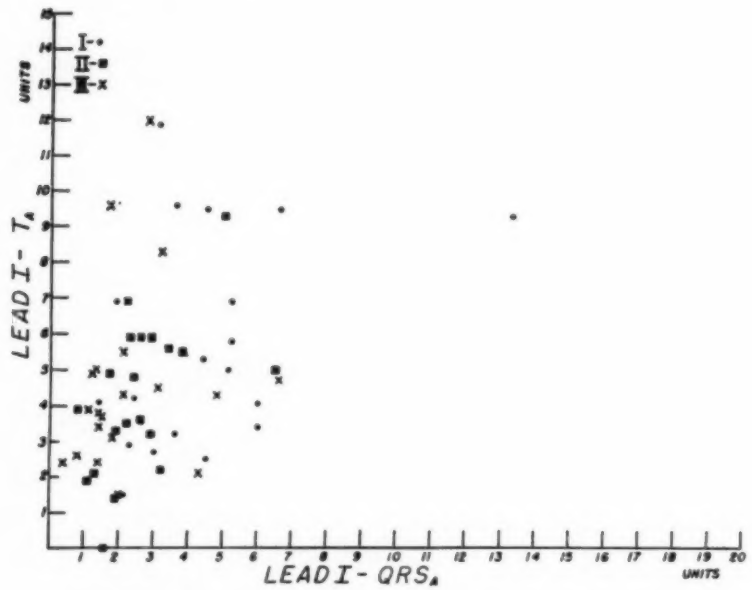


Fig. 5.—QRS area versus T area in Lead I. Same group and positional subgroups as in Fig. 4, A. Presence of some correlation.

In a later communication[16], more specific instructions for measurement of the spatial ventricular gradient (SG) are given. From inspection of the three standard leads, the loop in the frontal plane is drawn, and a standard spatial loop model with drawn-in axes of the spatial QRS area, of SG, and of SH placed so that the form of its shadow more nearly resembles the general form of the QRS loop derived from the limb leads. The error of measurement produced by drawing the loop from inspection must be large, but more fundamental objections can be made. This method is based on four assumptions: (1) that there is a standard contour of the spatial loop, (2) that there is a fixed relationship between electrical and anatomical axes, (3) that the three axes ($SQRS_A$, SG, SH) have a fixed position in the loop, and (4) that these three axes lie in one plane. All these assumptions are open to serious criticism.

Assumption (1): The rapidly growing material of electronically obtained loops in this and other laboratories demonstrates the great variability of these patterns and consequently the invalidity of any attempt of stereotyping.

Assumption (2): Fair correlation between anatomic and electric axes in the frontal plane in normal conditions has been shown,[17] but the serious deterioration of correlation in abnormal conditions[18,19] or for the horizontal plane even in normal conditions[17] vitiates the extension of the concept.

Assumption (3): This is probably the most vulnerable part in Ashman's concept of a spatial ventricular gradient. It implies that there is a correlation between contour of the loop and area vectors, but loop contour and time-voltage areas are entirely different aspects, and none is predictable from the other. Ashman's procedure implies also that SH, SG, and $SQRS_A$ can be represented by instantaneous amplitude vectors, since they are given fixed positions in the loop. If this were the case, area vectors would be superfluous altogether.

Assumption (4): This is entirely gratuitous without supporting experimental evidence.

Experience with the stereoscilloscope shows strikingly that the spatial QRS sheet is in itself highly curved in many individuals and that its "axis," and T axis, the anatomical axis and the spatial ventricular gradient axis can seldom be encompassed in one spatial plane even to the crudest approximation.

There is inevitably some tendency to confuse two different kinds of area in these analyses. The area under a curve of some potential component, as it varies with time, is completely different from the area included in the loop found by plotting two potential components as they vary parametrically with time.

The most logical, though arbitrary definition, of a spatial ventricular gradient applies the principle of construction of spatial mean amplitudes to areas. The direction of a mean vector is perpendicular to the axis of its null point and can be constructed from such points of zero or equiphasic potentials on the body surface. The null point for areas can be found on the body surface much as the null point for amplitudes is found.

Ashman and associates[20] came close to this idea when they determined separate null lines on the body for QRS and T areas from which the respective axes could have been determined as normals to the planes defined by the lines. However, they did not give a clear definition of a spatial ventricular gradient based on this approach, and no measurements of the gradient in spatial coordinates with this procedure were reported. This paper[19] preceded the description of technique of spatial gradient measurement[15] as discussed here.

Jouve and associates[21] measured the QRS and T areas in V_2 and V_6 as representative for the projection of the spatial gradient on the horizontal plane, in addition to the frontal plane, but their procedure ignores the different distance of V_2, V_6 and V_F from the heart.

2. *Normal Values of the Spatial Ventricular Gradient and Its Components.*—

a. *Method*: Two recently developed procedures were used to measure the spatial ventricular gradient: the electric area integrator and the spatial vector analyzer.[22] With this method, spatial vectors are reconstructed from their projections in direction and magnitude on the frontal plane, and from the direction of the horizontal plane projection at the level of the fifth intercostal space. Since the perpendicular projection of a vector is zero, spatial area vectors can be constructed when their null point is known, and the electrical integrator is an ideal method for null point determination. The null point location was defined as that point where the base line at the beginning and at the end of the deflection is at an identical level of integration, taking base line drifts into account by extrapolation (see Appendix II). Figure 6 shows in a typical example null points for QRS, T and QRS-T areas.

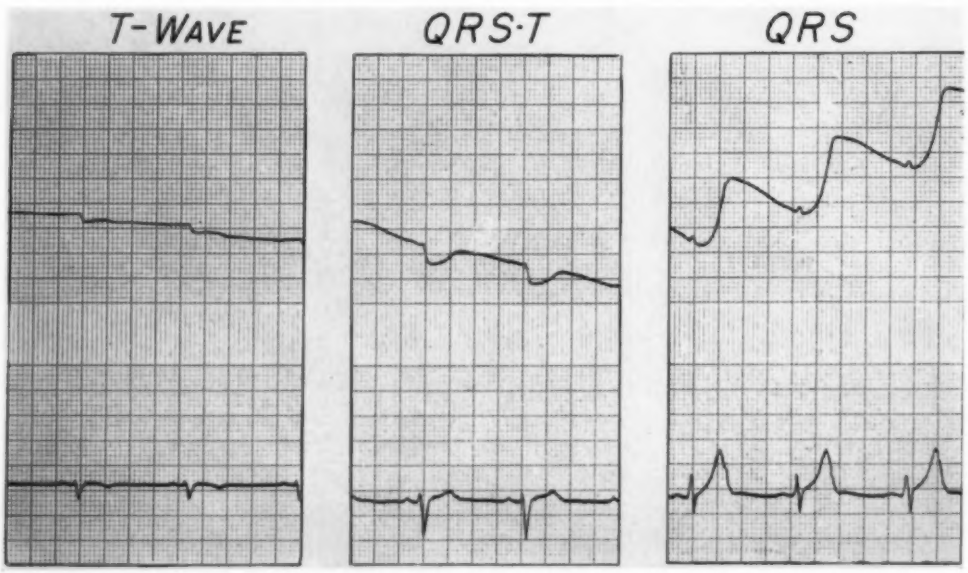


Fig. 6.—Upper Curves: Integrated areas; lower curves: electrocardiograms. T wave: Note total T wave area integration is zero, as indicated by identical level before and after the T area deflection. QRS-T: Null point is indicated by identical level (on the drifting base line) of start and end of QRS-T deflection. QRS: Null point for QRS complex.

The null points of QRS, T and QRS-T areas were localized along the fifth intercostal space, going from right to left. After the points were located, the protractor shown in Figs. 15A and B (see Appendix III) was used to record their precise location in the horizontal plane. The angular scale of this protractor corresponds with the horizontal plane scale of the vector analyzer.[22] This substitutes a fairly accurate measurement for an inaccurate estimate of angular position.

The spatial vectors are expressed in terms of the magnitude (Mag), the azimuth angle (H°), with the 0 to 180° line passing through a hypothetical center in the heart from left (0°) to right (180°), dividing an anterior positive and posterior negative hemisphere; the elevation angle V° between vector and a vertical projection through the center; the angle dA° between the spatial QRS and T area vectors, defined as positive when the T vector is in clockwise direction from the QRS vector.

b. *Results*: The values of twenty-three clinically apparently normal subjects were measured by means of this method. In five subjects, there was a discrepancy in the projection of QRS area vectors on the frontal and horizontal plane, and these subjects were not included in the tabulated data.

As independent vector measurements are made both in the horizontal and frontal planes, redundant data are obtained. It is consequently possible to appraise the measurements in terms of the internal consistency with respect to this redundancy. It is of interest that anomalies are much more frequent in area vector measurements than in mean amplitude vector measurements. This implies that area vectors measured in this manner are more poorly defined than mean amplitude vectors.

Table IV summarizes the data. The azimuth (H°), elevation (V°), Magnitude (Mag) of QRS_A, T_A, and QRS-T_A (VG), in means and standard deviations and dA°, the angle between the spatial QRS_A and T_A, are listed. The group is too small to establish normal standards but sufficient for orientation.

TABLE IV. SPATIAL VECTORS OF QRS, T AND QRS-T AREAS (VG) IN 18 NORMAL YOUNG MEN (GROUP A) COMPARED TO THE SPATIAL VECTORS OF THE MEAN QRS AND T AMPLITUDES IN THE SAME GROUP AND IN ANOTHER GROUP OF 35 YOUNG MEN (GROUP B)

GROUP	ITEM	H°		V°		MAG		dA°	
		M	S. D.	M	S. D.	M	S. D.	M	S. D.
					AREAS				
A	QRS	−27.9	19.10	31.6	13.04	10.7	5.44		
	T	47.0	15.04	54.9	17.69	17.1	10.86	53.8	11.74
	QRS-T	23.9	17.90	36.2	15.50	24.3	15.55		
					MEAN AMPLITUDES				
A	QRS	−24.4	19.48	31.8	11.82	12.2	1.22	53.8	15.18
	T	46.8	15.31	57.2	16.51	4.2	1.18		
B	QRS	−27.8	18.52	23.6	17.02	12.5	5.29	46.2	14.55
	T	35.5	14.67	53.3	14.50	4.0	1.09		

H° = azimuth, V° = elevation, Mag = magnitude, dA° = angle between spatial QRS and T, M = means, S. D. = standard deviations.

These data are compared to the spatial vectors of the mean QRS and T amplitudes of the same group (A) and of another comparable age group (B) of thirty-five young men. The means and standard deviations of azimuth (H°) and elevation (V°) of mean amplitude and area vectors are quite similar, as might be expected from the close correlation between amplitude and area measurement in Lead I (see Section IV). The standard deviation of dA° is somewhat smaller for the area vectors than for the amplitude vectors, but the difference was statistically not significant. The possibility of a somewhat smaller variability of dA° for QRS_A and T_A might deserve further exploration.

The magnitude of the T area vector is significantly larger than the magnitude of the QRS area vector, probably due to drifts during the S-T segment. The significantly higher (5 per cent level) standard deviation for the magnitude of the T area, compared to the QRS area, might be due to the same reason. The standard deviation for the magnitude of the QRS-T area is considerably higher than the standard deviation for the magnitude of QRS_A, and the difference is statistically highly significant. The standard deviation in percentage of the mean is about the same for the spatial T and QRS-T area (64 per cent).

The magnitude of the QRS and T mean amplitude vectors is, of course, expressed in different units from that of the area vectors, but their standard deviations are not only absolutely, but also in per cent of the means, significantly smaller. This indicates that the amplitude vectors are preferable for differentiation between normal and abnormal.

There is a statistically highly significant correlation between the spatial QRS and T area magnitude (Fig. 7), ($r = 0.586$), and this relationship may be expressed by a regression equation $T_A = 6.43 + 1.1\ QRS_A$. It is of interest that the slope implied by this equation is close to 45°.

The absence of correlation in the frontal plane accompanied by some correlation in Lead I and good correlation in the spatial QRS and T areas requires some explanation.

The deterioration of correlation in the frontal plane can be ascribed to compounding of the individual uncertainties in the components taken from Leads I and III to constitute the frontal plane projection. The spatial vector on the other hand is not intrinsically variable with heart position as are its projections on a plane, and therefore this quantity best displays any real consistency of QRS and T area vectors.

3. *Electrical Measurement of the Spatial Vector Ventricular Gradient.*—The algebraic time voltage area of the manifest QRS-T pattern in the frontal plane has been defined as the ventricular gradient. Extension of this concept to a spatial equivalent capable of quantitative measurement requires first a resolution of certain ambiguities inherent in the frontal plane gradient concept and secondarily an elaboration of these ideas to permit of unambiguous tridimensional vector analysis.

Detailed analysis of this problem and its instrumental solution will be undertaken in another publication, but an outline of the approach can be presented here.

a. *Normalization and Orthogonalization*: It is evident that the ordinary leads represent unequal and asymmetric components of heart electrical activity and that consequently the standard leads can only approximately be thought of as equilateral triangular components of a central vector. This system, further, is exclusively concerned with the frontal plane. By judicious choice of electrode positions and proper mixture and attenuation of the potentials taken from at least four and preferably seven positions on the body, components representing nearly correctly scaled mutually perpendicular components of heart dipole current can be obtained. These are substituted in this treatment for the more conventional lead components. In effect we obtain three potential differences from a weighted central terminal unit proportional, respectively, to pure horizontal, vertical, and sagittal heart dipole currents.

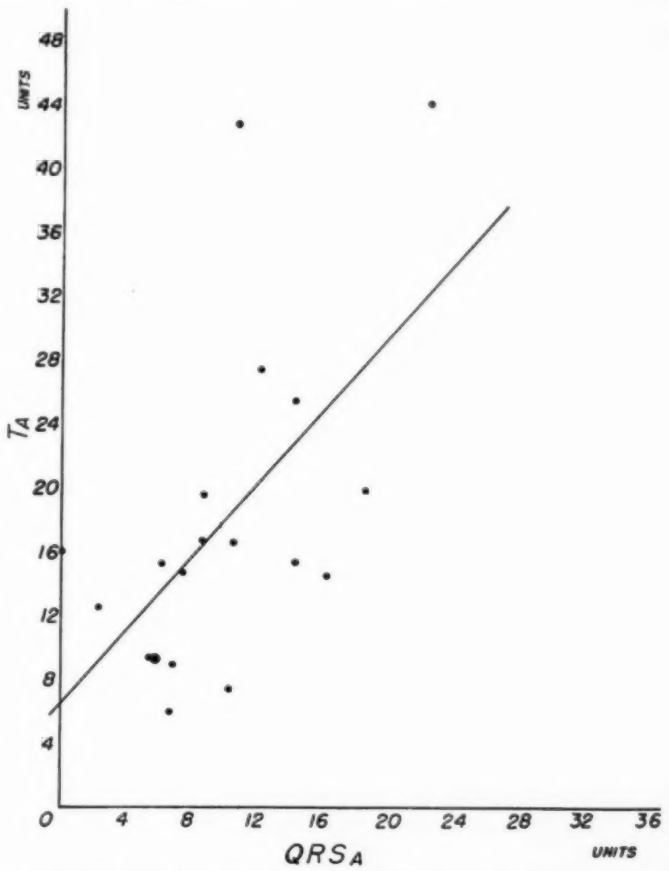


Fig. 7.—Spatial QRS area versus spatial T area. Highly significant correlation.

b. *Precise electrical definition of a frontal plane "Ventricular Gradient"*: The conventional definition of ventricular gradient contains the implicit assumption that there exists some unique axis along which each of the heart complexes of electrical activity can be thought of as concentrated. While this is often reasonably meaningful for a normal T complex and is not entirely undefined for a normal

QRS loop, it is quite undefined in the case where these loops are multilobed or of other open shapes.

The physiologic idea behind the ventricular gradient concept is preserved if one substitutes for the simple major geometrical axis of the pattern, the vector quantity obtained by integrating separately with respect to time, the algebraic value of the horizontal and the vertical components of the frontal plane potential. These two quantities $V_x = \int_0^{t_b} X dt$ and $V_y = \int_0^{t_b} Y dt$ where X is the x component and Y the y component of heart potential may be regarded as the components of a vector in the frontal plane. These can then be added vectorially to yield a quantity having some vector characteristics which may be accurately measured. This vector ventricular gradient corresponds practically with the commonly used ventricular gradient and is unambiguous.

c. *Extension to spatial case*: This procedure can obviously be extended to the spatial case with no difficulty whatsoever beyond obtaining a sagittal or Z component. Adding this vector component defines a spatial ventricular gradient which is accurately defined and easily measured with modern electronic equipment. It should be especially noted that this quantity in the ideal case would not be magnitude sensitive to axis shifts if they were unaccompanied by other physiologic changes while the frontal plane ventricular gradient would be especially sensitive to them in the event of actual spatial ventricular gradient orientation approaching the perpendicular to the frontal plane.

Instrumental detail of this procedure is included in Appendix I.

IV. CORRELATION BETWEEN AMPLITUDE AND AREA MEASUREMENTS

The significant correlation between the spatial QRS and T areas is paralleled by an equally significant correlation between the mean spatial QRS and T amplitudes in another group of fifty-eight normal subjects[13] with dA° between 45° and 65°. The dA° of this group falls within the same range. This means that the mean spatial QRS amplitude demonstrates this fundamental relationship as well as the spatial QRS and T areas. One questions then what additional information can be expected from area measurements. The substantial time involved in area measurements makes this of practical importance.

Figure 8 shows a scatter diagram of the T area versus T magnitude in Lead I in sixty normal men. The area was measured carefully by counting squares with the aid of a magnifying glass and is expressed in Ashman units (1 unit = 4 microvolt seconds). The correlation is excellent, with $r = 0.88$, a t-value of 14.15 corresponding to $p = 0.001$. The correlation between QRS amplitude and QRS area in Lead I was $r = 0.81$, which was also statistically highly significant ($t = 10.61$). The somewhat lower correlation for QRS than for T is explained by the fact that the QRS area is usually a sum of positive and negative areas, which increases the error of measurement, while T is usually unidirectional. We repeated the measurements in another sample of fifty-eight normal men with identical results (T amplitude versus T area: $r = 0.88$; QRS amplitude versus QRS area: $r = 0.83$). The actual correlation, of course, would be still higher if the technical errors of measurement could be eliminated. This means that in

normal electrocardiograms the area is fairly predictable from the amplitude, and that the measurement of areas adds little to the measurement of amplitudes. This is probably true also for many abnormal electrocardiograms with smooth and symmetrical contour, but, of course, not for electrocardiograms with ventricular conduction defects.

There is evidence that incidence of abnormal QRS, T, and QRS-T area axes in the frontal plane in patients is greater than the incidence of abnormal magnitude of the areas. It was suggested (p. 130) that in most cases the mean amplitude axes also would be abnormal in these cases. The results of a statistical analysis are shown in Table V for the azimuth H° of QRS and T areas and amplitudes. The correlation coefficient is extremely high both for the QRS complex and the T wave, and the mean differences and their standard deviations are very small. This means that the null point for areas can be determined with sufficient accuracy (0.75° error for QRS and 3.7° for T) from the mean amplitudes. This is true only for diphasic deflections and reasonably smooth and symmetrical contours, but valid for the great majority of normal people and also for many abnormal electrocardiograms.

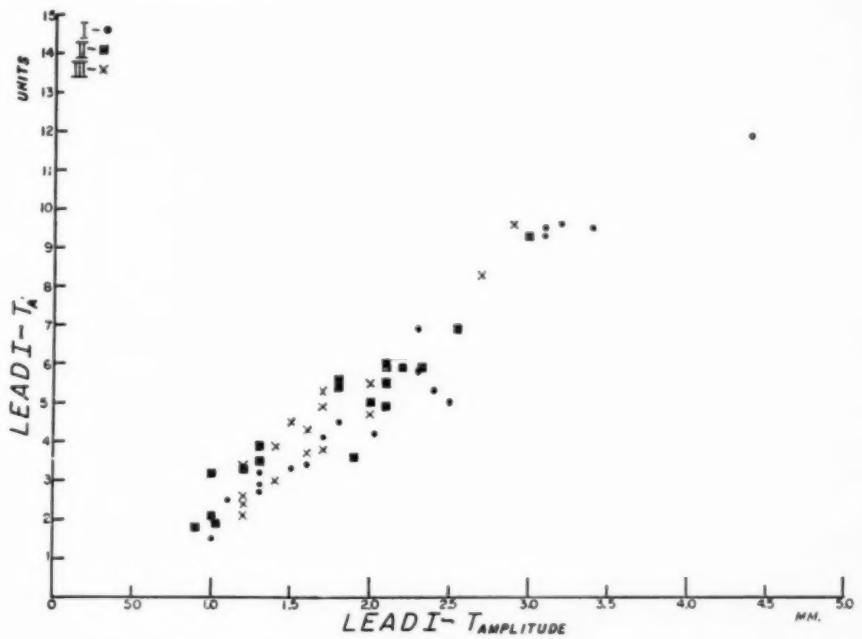


Fig. 8.—T_I amplitude (abscissa) versus T_I area (ordinate): perfect correlation.

The results substantiate the prediction that in most cases with abnormal axes of area vectors the amplitude vector axes also will be abnormal.

The correlation of dA° between spatial QRS and T areas versus QRS and T mean spatial vectors is of interest, because this is the last step of the spatial vector analysis and will show up all accumulated errors. In view of this situation, the correlation of r = 0.75 is quite good (Table V).

V. DISCUSSION

The material presented is concerned mainly with the variability of the ventricular gradient and its components among normal individuals as this variability is more important for differentiation between normal and abnormal than is the intraindividual variability.

The absence of correlation between the manifest frontal QRS and T areas within the wide normal scatter means that no prediction of the T area from QRS area is possible in normal subjects and consequently none is to be expected in patients. In other words, the frontal plane ventricular gradient (which is the only one generally measured) does not permit a safe differentiation between primary T changes (independent of QRS with changed gradient) and secondary T changes (dependent on QRS, with constant gradient).

TABLE V. COMPARISON OF THE AZIMUTH (H°) OF QRS AND T MEAN AMPLITUDE AND AREA VECTORS, AND OF THE ANGLE dA° BETWEEN MEAN SPATIAL QRS AND T AMPLITUDE VECTORS VERSUS SPATIAL QRS AND T AREA VECTORS. MEANS (M), MEAN DIFFERENCES (Δ) AND THEIR STANDARD DEVIATIONS (S.D.) IN 20 NORMAL MEN

	H°		H°		dA°	
	QRS AMPL.	QRS AREA	T AMPL.	T AREA	AMPL.	AREA
M	−24.33	−24.78	45.45	46.30	53.78	54.22
Δ		− 0.44		+ 0.85		+ 0.44
S.D.		1.68		3.25		10.04
r		0.996		0.981		0.751

Such differentiation might still be possible if the normal range limits of the ventricular gradient were relatively narrow compared to deviations in abnormal conditions, but this is not the case. The large interindividual variability of the ventricular gradient can be anticipated from theoretical considerations. Again, there could be a correlation between the degree of myocardial involvement producing primary T changes (such as coronary insufficiency) and the deviation of the gradient. The views of various authors are controversial, but the bulk of evidence speaks against such correlation[10,23-26] (see also Section II, 3).

It is possible that the axes of the ventricular gradient and its components (QRS and T area) are of greater diagnostic significance than the magnitude. In the existing literature the incidence of abnormal area axes in patients was indeed greater than was the corresponding abnormality in magnitude. However, it should be emphasized that in Wilson's original concept the magnitude of the ventricular gradient is by far the more important criterion. He stressed the point that the gradient is reasonably constant even at extreme variations of the QRS and T area axes. Since the overlap in measured values of the gradient magnitude for normals and abnormals is practically complete, it is hard to assign any significance to changes of the gradient axis. The QRS and T area axes correlate quite well in most cases to the mean QRS and T amplitude axes, so that little additional information from area measurements can be expected (see Section IV).

There is no doubt that statistically significant mean differences in the VG exist between normal groups and groups of patients with various lesions: myocardial infarct,[12] left bundle branch block,[11] cor pulmonale.[10,27] This group difference is of little value, however, for the individual patient even though it may be of interest for the description of a lesion.

The frontal plane gradient, like any frontal plane vector, involves a potentially large projection error which is not involved in the determination of the spatial gradient; this point is illustrated by the highly significant correlation between the spatial QRS and T areas.

The strong positive correlation always found between the spatial QRS and T areas demonstrates that the ventricular gradient is really a poor unit for combining these two measurements into a single quantity for this quantity implies a strong negative correlation. Were the gradient sensibly constant in normal individuals, we would expect large negative T areas to accompany large positive QRS areas or we would at least expect the T area to decrease as the QRS area increases. This is never found in normal subjects.

While the material of Fig. 7 is not adequate to permit exact determination of the average relationship between the spatial QRS and T areas, it is obvious that a near linear relation exists between them with a + slope approximating unity. It would be entirely feasible to determine the appropriate parameter values in a large material and thus replace the ventricular gradient concept with a substitute which is in accord with experimental evidence. The limited availability of the electrical equipment necessary for this work has precluded immediate completion of such a study prospect.

The utility of the ventricular gradient for evaluating intraindividual variability is better. Much of the variability between individuals is structural and consequently constant within the same individual under ordinary conditions. Significant intraindividual variations have been found in normal exercise,[3,28] tachycardia,[3] body position,[3] orthostatic response,[29] and abnormal conditions such as glomerulonephritis,[16,30] pericarditis,[31] fever,[32] myocardial infarct.[33] However, no normal standards for intraindividual variability have yet been made available, and no attempts were made to compare the variability of the ventricular gradient and its components with the variability of mean or instantaneous amplitudes. This may be illustrated by Ashman's[30] case of a patient with glomerulonephritis; two electrocardiograms were within normal limits, but T_1 and T_2 were higher in the second electrocardiogram taken when the blood pressure (which was elevated at the time of the first electrocardiogram) had returned to normal. There were no essential changes of the QRS complexes. Ashman concludes that the gradient analysis permitted diagnosis of the first electrocardiogram as abnormal. By using the normal limits of intraindividual T-amplitude[34] variability, the same conclusion could have been made without gradient analysis and on a statistically more reliable basis. In general, our results amplify Katz's[35] statement: ". . . . . I see no need to use the ventricular gradient in clinical electrocardiography."

Our criticism of the ventricular gradient does not apply to time voltage area measurements in single leads, which may be very valuable for analysis of some abnormal conditions as shown by Schaefer.[6] The usefulness of time integrated spatial area vectors remains to be explored.

SUMMARY

1. The theoretical basis of the ventricular gradient concept is re-examined.

2. The effect of changing pathway of ventricular activation is analyzed in Wilson's experiment and in a corresponding human case.

3. Normal limits for the magnitude of the ventricular gradient are calculated and tabulated for a group of 107 healthy men and for corresponding material available from the literature.

4. Analysis of the literature reveals that very few cases even with advanced myocardial involvement exceed these normal limits.

5. No correlation is found between the manifest QRS and T areas in any of three different experimental normal groups even when the area measurements are made by means of an electronic integrator, which is described in appendix II.

6. Analysis of the existing literature on the spatial gradient reveals that no adequate method of measurement has yet been described.

7. A simple method for measuring the spatial ventricular gradient based on determination of a null point for the QRS-T area at the fifth intercostal space is developed.

8. Some representative normal values of the spatial ventricular gradient and its components are given.

9. A strong positive correlation between the spatial QRS and T areas is found in contrast with the negative correlation implied by conventional ventricular gradient theory.

10. A theoretically more satisfactory definition of a spatial ventricular gradient is proposed based on the stereovector theory.

11. Technical electronic means for instananeous determination of the spatial ventricular gradient are described.

12. The results do not encourage further use of the frontal plane ventricular gradient in clinical electrocardiography. The value of its spatial correlate remains to be proved.

We wish to thank Dr. Richard V. Ebert for his interest in the progress of this work.

APPENDIX I

APPLICATION OF THE RADIAL SHEET MODULATOR AND SVEC TO SPATIAL VECTOR VENTRICULAR GRADIENT MEASUREMENT

In earlier sections of this paper it has become evident that the ventricular gradient has a spatial vector counterpart (SVG) related to the spatial vector electrocardiogram much as the ordinary frontal plane ventricular gradient is related to the simple electrocardiogram.

We may define this spatial vector gradient as that vector whose components are, respectively, the horizontal, the vertical, and the sagittal components of the electrocardiogram each integrated algebraically with respect to time over an entire heart cycle.

Taken together these components define a direction and magnitude which can be called the spatial vector gradient and can be thought of as a vector quantity expressing the "gradient" of the electrocardiographic voltage integral residue over a heart cycle.

In the stereovectorelectrocardiographic (SVEC) system which presents the spatial vector electrocardiogram directly in a visual stereoscopic display (Schmitt),[26-28] it is relatively easy to include this new spatial vector gradient concept as an added feature of the normal presentation.

In its simplest form the stereovectorelectrocardiographic presentation displays a spot in space which traces out in time sequence the space locus of the tip of the stereovectorelectrocardiographic vector thus forming a characteristic three-lobed figure, the lobes representing, respectively, the P, the QRS, and the T complexes.

On this presentation it is often convenient to superimpose intensity modulation to mark time intervals and also perhaps trace motion direction. It is much more effective, however, to modulate the trace radially on a time basis such that the lobes become radially shaded sheets in which curvature and magnitude are easily perceived, Fig. 9 (Schmitt).[39]

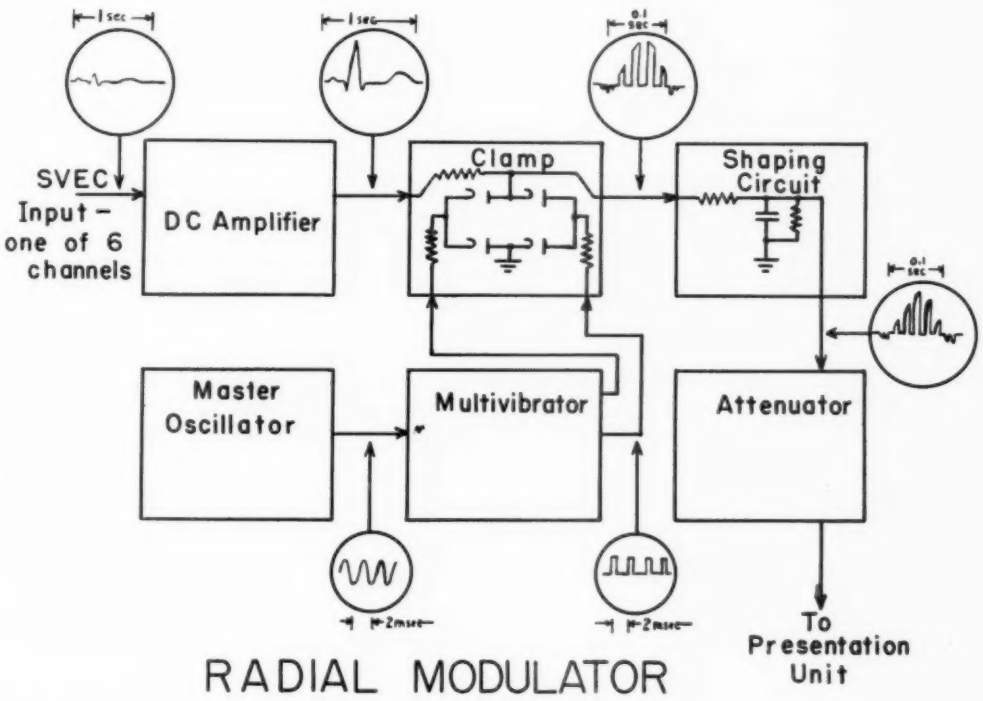


Fig. 9.—Functional block diagram of radial modulator system. Circles illustrate typical oscilloscopic wave forms at indicated positions in the circuit.

If the "zero" to which these radial modulations are referred is the "rest potential" of the T-P interval, the figure is the ordinary stereovectorelectrocardiographic ideal. The stereovectorelectrocardiographic instrument can, however, be so adjusted that the "zero" in each component direction makes the time-potential integral equal to zero as averaged over the entire heartbeat cycle. During the relatively long T-P interval the stereovectorelectrocardiographic oscilloscopic spot will not rest at the origin of coordinates. Instead it will stop at a position which represents vectorially a set of potential components just equal and opposite to those of the spatial vector gradient. In effect, the instrument automatically biases the rest position so that the whole pattern has no residual area. The steady state bias needed to accomplish this equalization is one equal and opposite to the spatial vector gradient. This value can be read off easily during the T-P interval when no physiologic activity is assumed to exist. With radial modulation, then, the picture during the T-P interval will be that of a short straight radial line pointing just opposite to the spatial vector gradient and proportional to it in length.

Dimensionally the line represents a voltage while the spatial vector gradient must be a voltage multiplied by time. This apparent anomaly is resolved when one realizes that the indicated spatial vector gradient voltage is that voltage which for a whole beat equals the time integral of the vector gradient components. The numerical magnitude of the spatial vector gradient thus is obtained by multiplying the measured voltage by the duration of the beat. Thus if the potential difference is read in millivolts and the heart beat duration in milliseconds, this direct product will be in microvolt seconds. To devise a quantity equivalent to Ashman's unit of 4 μv. sec. we can write down the formula

$$SVG = \frac{V_{RR} \times 1000 \times 60}{R_H \times 4} = \frac{15000 V_{RR}}{R_H}$$

where V_{RR} is the observed residual resting voltage in millivolts, R_H is the heart rate in beats per minute and SVG is the magnitude of the spatial gradient in 4 μv. second units. The factor of 1,000 is introduced to convert V_{RR} to microvolts, the factor of 60 to reduce R_H to beats per second while the factor of 4 introduces the necessary modification to produce units of the same size used by Ashman on the basis of the unit square on ordinary electrocardiographic recorder paper. If simple microvolt second units are desired, the multiplier becomes 60,000 instead of 15,000.

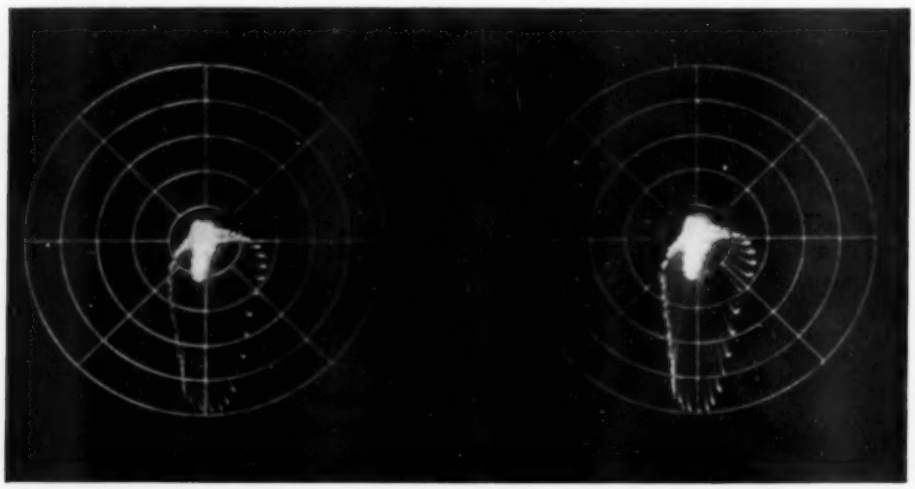


Fig. 10.—Direct visualization of spatial ventricular gradient using radial sheet modulation of the stereovectorelectrocardiogram. The figure should be viewed with a standard stereoscope to appreciate the spatial configuration of the spatial vector gradient in relationship to the QRS and T complexes. The picture was taken from a left shoulder view at elevation +53°, azimuth 102° looking nearly at the flat of the QRS loop. The T and QRS axes are nearly in coincidence. The warpage of the QRS sheet is clearly visible. The negative spatial vector gradient vector is seen to protrude upward at "eleven o'clock" slightly behind the graticule plane. Its amplitude can be read off from the rings which represent one-half millivolt intervals.

It is seen from this formula that for a typical SVG of 20 units and a heart rate of 75, $V_{RR} = \frac{20 \times 75}{1500} = 0.1$ or one tenth millivolt, a quantity which is just easily measured. Technically, it is easier to use the zero area reference required by this presentation than to use the intuitively more appealing T-P reference. Introduction of a single long-time-constant blocking condenser circuit into the amplifier train will effect this result, and this blocking greatly reduces the problem of drift over that experienced with the D.C. amplifier train needed to display the more ideal zero T-P reference stereovectorelectrocardiogram. Figure 9 shows a block functional diagram of this device, and Fig. 10 illustrates the type of record obtained by this means and must, of course, be viewed stereoscopically to be fully appreciated as a spatial display. The short heavy line indicated by the arrow represents the negative equivalent to the SVG.

It should be noted that by this method the whole P wave is included in the analysis while in the ordinary analysis only those portions of the auricular complex submerged in the QRS are included. The influence of the P wave is, of course, normally slight.

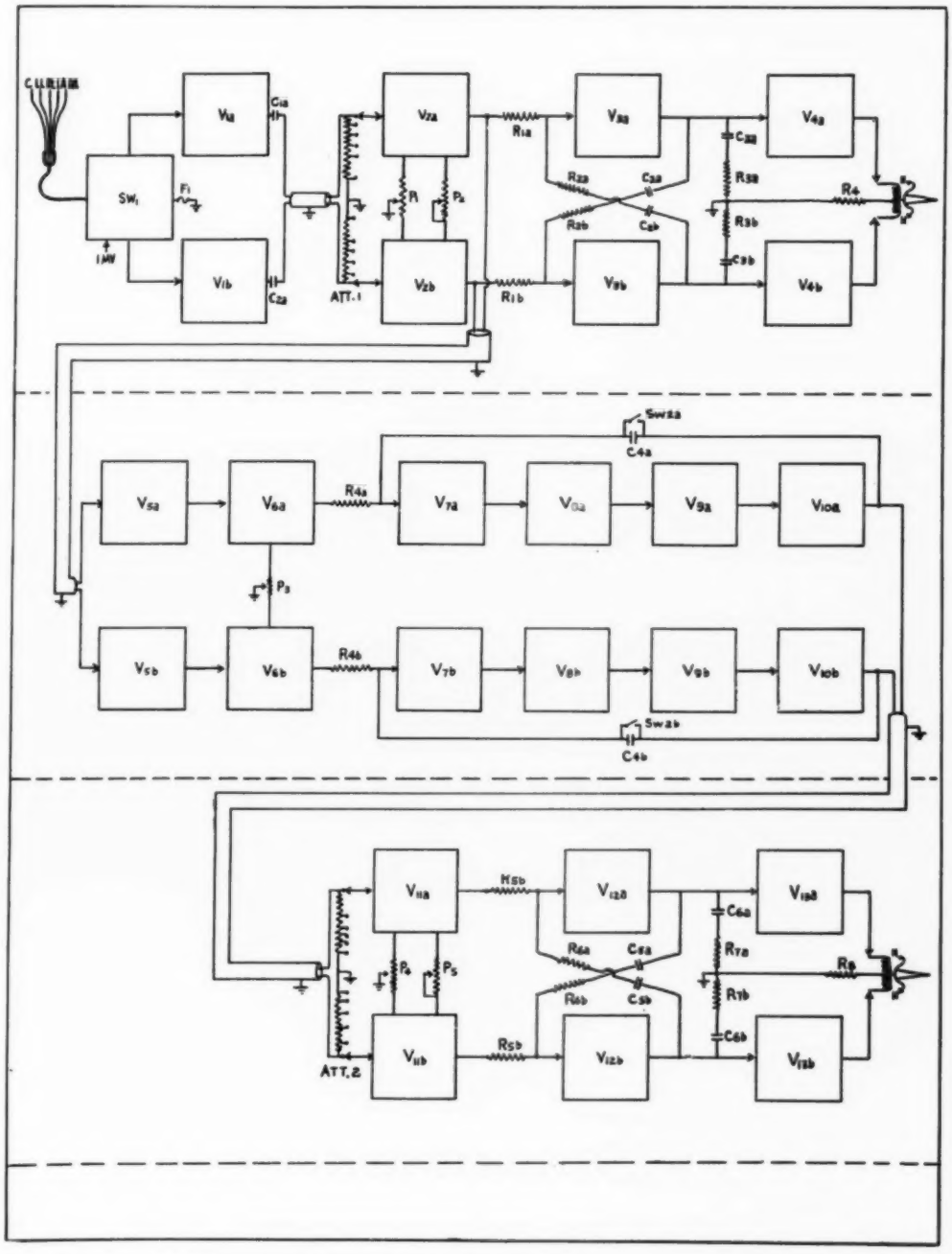


Fig. 11.—Block Diagram of Integrating and Recording System. Top section preamplifier, center section integrator, lower section recorder. Preamplifier and recorder are modified standard Sanborn units. Integrator amplifier stages V_7, V_8, V_9 are cathode cross-coupled.

V_1, V_2, V_3, V_{11}, V_{12}—6SL7; V_4, V_{13}—6V6; V_5, V_9—12AT7; V_6—12AY7; V_7, V_8—12AX7; V_{10}—12AU7.

SW_1—lead selector; SW_2—discharge relay; P_1, P_4—centering; P_2, P_5—gain; P_3—D.C. balance; F_1—patient fuse 0.005 amp.; ATT 1—1.5 meg.; ATT 2—5 meg.

R_1, R_5—470k.; R_2, R_6—6.8 meg.; R_3, R_7—10 k.; R_{4A}, R_{4B}—3 meg.; R_4, R_8—2 k.; C_1—1 mfd.; C_2, C_5—470 mfd.; C_3, C_6—0.01 mfd.; C_4—0.1 mfd. poly.

APPENDIX II

ELECTRONIC AREA INTEGRATOR

Several electrical methods are used for time integration by which the ventricular gradient components required in the preceding studies could have been obtained. The feedback type condenser integrator is, however, the simplest circuit which will give adequate accuracy and consequently it was the one used. Its mode of operation is well described in the literature[40] and need not be reviewed here. Suffice it to say that this integrator depends mainly upon availability of a condenser which follows the theoretical $q = cv$ law with sufficient accuracy, upon inclusion of sufficient feedback to make the condenser voltage practically negligible with respect to the signal voltage, and upon provision of adequate amplifier bandwidth and stability to reduce to negligible proportions the tendency for distortions and spurious drifts.

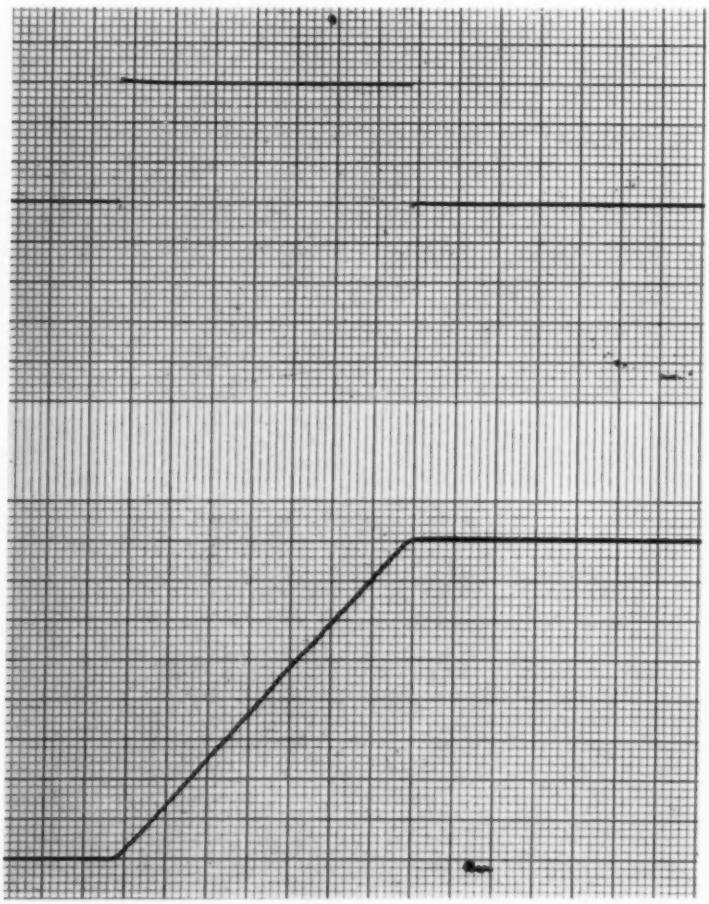


Fig. 12.—Calibration curve of area integrator. Upper tracing: Square wave input; recorded with Sanborn direct-writer. Lower tracing: Area integration. Area above base line in upper tracing is converted into amplitude in lower tracing.

The actual apparatus as represented in block diagram form by Fig. 11 consists of a preamplifier system, an integrator proper, and a conventional recorder. The preamplifier was essentially that of a standard Sanborn Cardiette unit, slightly modified to make its frequency characteristic suitable for driving the integrator. The integrator is a balanced cathode cross-coupled

three-stage direct-coupled amplifier with cathode follower output feeding back into a polystyrene integrating condenser. A second complete Sanborn unit serves as output amplifier and recorder. Approximately zero setting and initial bias controls are incorporated into the integrator section.

Figure 12 illustrates typical calibration runs with a rectangular standard step wave input. The first record shows the slightly underdamped direct recorder response and the second the near ideal linear rise from the slope of which is calculated the time-potential integral calibration constant.

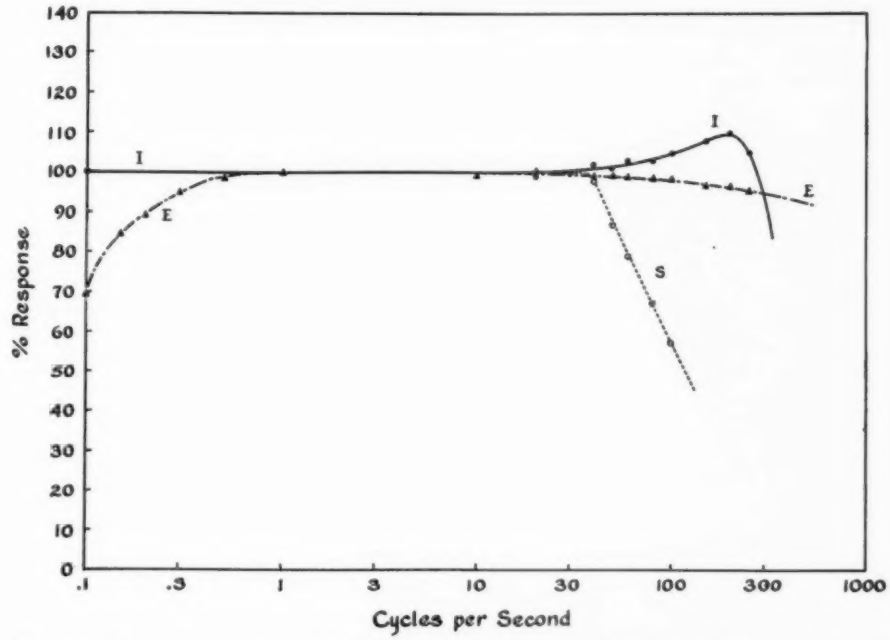


Fig. 13.—Frequency response of the area integrator at 0.1 to 1,000 c.p.s. (abscissa), in per cent of response at 20 c.p.s. = 100 (ordinate). I = product of output voltage × frequency. The prolongation beyond the last measured point at 1 c.p.s. to 0.1 c.p.s. is extrapolated. E = Instrumental response excluding writer; S = Over-all response including recorder (direct-writer).

It is usually thought that no important electrocardiographic potential components lie in the frequency range above 200 c.p.s. and consequently the instrumental response curve *E*, Fig. 13, which falls only to 95 per cent at this frequency is considered fully adequate, especially in consideration of the inverse frequency sensitivity characteristic of integrators. Low frequency response is that of the standard recorder.

Because the time integral of a sine wave contains a multiplying term 1/f where f is the frequency, it is customary to test integrators by plotting their output voltage multiplied by frequency against frequency. This product is plotted as Curve I and shows good low frequency response along with a rising high frequency pre-emphasis introduced to improve recorder response. Curve S shows the over-all system response including the recorder.

As a blocking condenser is included in the preamplifier circuit to eliminate steady state skin potentials, the integrator does not have an intrinsic absolute zero reference potential, and an arbitrary reference level must be introduced manually. This reference is normally taken at the level of the T-P interval.

As the results recorded from the integration system depend critically upon the arbitrarily chosen "zero" voltage level, drifts and other factors which influence this quantity must be considered and carefully controlled. Indeed, an error of 1/10 millivolt in setting the zero level will produce typically an error of over 100 per cent in the recorded QRS-T area. This error is not unique to the electronic integrator but corresponds to proper choice of T-P base line when meas-

uring QRS-T area values graphically. Here it should be noted that an error in base line choice equal to half the usual broad trace width will produce a similar error.

Because D.C. skin potential is adequately blocked by a resistor-condenser coupling in the circuit, this factor does not introduce complications. Variations in the skin potential with time do, however, become displayed as drifts. For all slow potential changes of this sort as well as for preamplifier drifts which are superimposed upon them, the blocking condenser and its subsequent resistance load become a differentiating network so that a steadily increasing skin potential is rendered as a constantly displaced zero level at the integrator. This effect can consequently be totally eliminated as part of the zero setting process. A drift voltage which changes its rate of drift linearly (i.e., a parabolically changing drift potential) displays itself as a constantly changing zero level and cannot conveniently be compensated, although it can be corrected by appropriate analysis of the records. An accelerating drift rate yields records which are nearly impossible to analyze, and fortunately it is seldom found if electrodes are well applied. Amplifier drift is ordinarily a lesser factor than electrode polarization and physiologic drift.

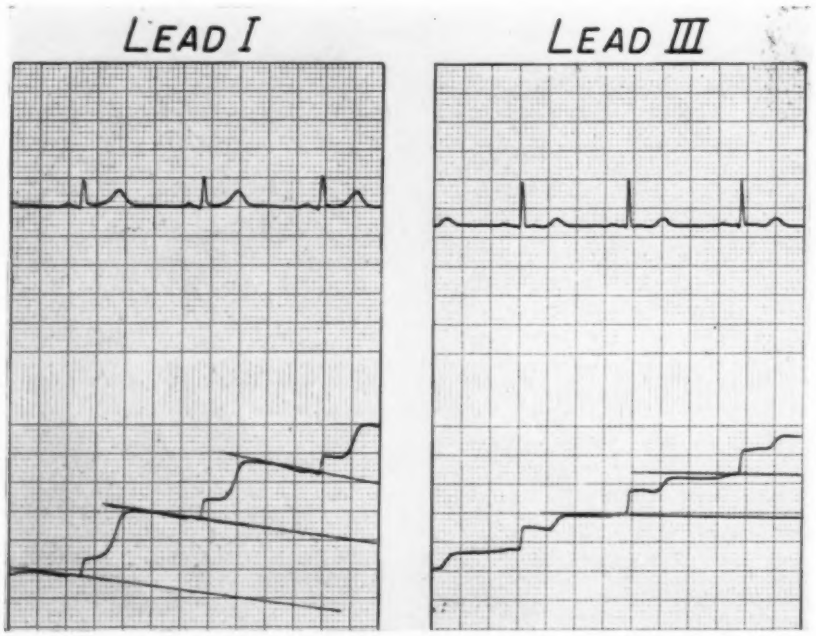


Fig. 14.—Upper Curve: electrocardiogram: Lower Curve: area integration with base line extrapolation. Lines 1 and 2 are parallel, indicating measurable complex. Lines 2 and 3 are not parallel, indicating that the second complex should be discarded for measurement. The parallel lines in Lead III show one measurable complex. Note the small influence of the P wave area.

Choice of choosing proper sections of the electrocardiogram make it easy to find portions where there is no drift or where the drift may be considered as a simple base line shift. In this latter case the base line is rising in a linear fashion with time. As the T-P interval was considered the base line in the present study, one defines the sloping portions of the integrated tracing corresponding to the T-P interval of the simultaneous electrocardiogram as zero integral (Fig. 14). This portion of the integrated tracing is extended with a ruler and vertical distances from it represent the true integral. This method, of course, corrects only for first order drift. If high order of drifts exist, this is obvious by inspection and the questionable portion of the tracing should be ignored.

It was found that a slow cyclic change in the base line which corresponded fairly well to the respiratory cycle occurred in all cases. The cyclic shift of the base line was noted to the greatest extent in lead three. It could not be entirely accounted for by respiration, because breath-holding did not eliminate it.

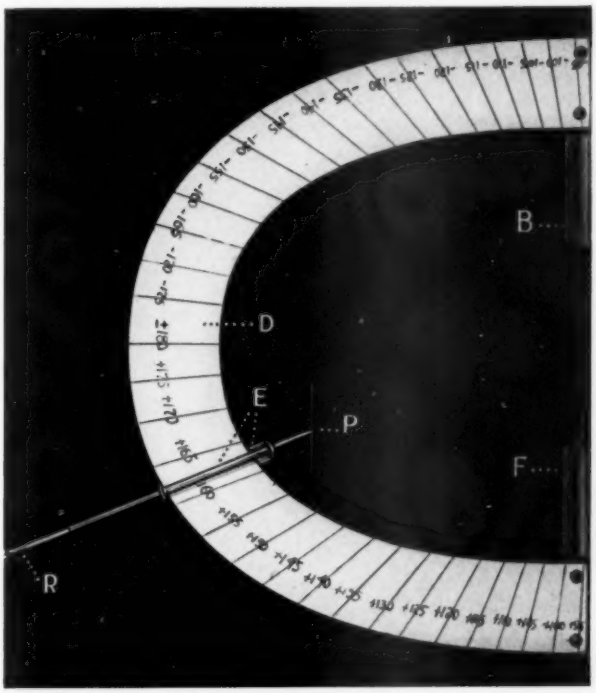


Fig. 15A.—Protractor for measurement of the null point in terms of azimuth (H°). Use for right side of the chest. Description see text.

Fig. 15B.—Reverse side of the protractor for use on the left side of the chest.

APPENDIX III

PROTRACTOR FOR LOCATION OF THE NULL POINT

Figure 15A shows the protractor for use on the right side of the chest with the scale *D* from +90° (front) or −90° (back) to ±180°, and Fig. 15B shows the reverse side for use on the left side with the scale *D* from +90° or −90° to 0°. This scale corresponds to that of the horizontal plane of the spatial vector analyzer, which includes a correction for the asymmetric position of the heart in the chest. The metal ends *F* (front) and *B* (back), movable in a slot, are set on the mid-sternal and mid-back line at the level of the fifth intercostal space. The set-screws (shown in Fig. 15B) are tightened and the protractor is kept firmly in this position. A pointer *P* is movable around a screw *S* as well as in longitudinal direction through a tube *E* (by means of a knob *R*) with sufficient friction to keep it in place. *P* is moved to the null point on the chest, as determined with the electrical integrator, marked with pencil, and by movement around *S* put in a position to parallel the radii on the scale in that segment. The error of reading the angle on *D* is only about 1°.

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Book Reviews

DAS ELEKTROKARDIOGRAMM BEI DYSTROPHIE ALS BEITRAG ZUR PHYSIKALISCH-PHYSIOLOGISCHEN ANALYSE DES ELEKTROKARDIOGRAMMS. By F. P. N. Schennetten. Berlin, 1951, Akadmie Verlag, 53 pages with 21 figures.

The first part of the book consists of a rather superficial statistical analysis of the electrocardiograms in 238 patients with different degrees of malnutrition and very different clinical backgrounds. The results are not essentially new.

The second part of the book consists of a series of experiments with changing external resistance and capacitance. From the results it is concluded that the low voltage in malnutrition is mainly due to a degeneration of the fat tissue surrounding the heart which decreases the resistance in the electrical field.

The general standard of the book is characterized by statements that the first sign of atrioventricular block is a shortening of the P-R interval, and that "the electrocardiographic changes (in malnutrition) were irreversible in most patients who died."

There is no justification for publication of the material as a book, and not much for publication at all.

E. S.

THE HEART BEAT. By Aldo A. Luisada, New York, 1953, John Hoeber, Inc., Medical Book Department of Harper & Bros., New York, 527 pages, 273 figures.

This volume is devoted to a summary of the many different methods of graphic recording of cardiac activity in health and disease. The first portion of the book is devoted to normal and abnormal findings obtained by phonocardiography, ballistocardiography, recordings of the venous and arterial pulses, roentgenkymography, electrokymography, precordial and epigastric cardiography, electrocardiography, and vectorcardiography. There are also sections dealing with pulsations of the liver, cardiac catheterization, and with respiratory tracings, including pneumography and pneumotachography. The section devoted to phonocardiography is especially noteworthy and well written. Because of the scope of the material covered, the various chapters necessarily are condensations of present knowledge concerning these methods of graphic recording of the heart beat and of respiratory activity. There is, however, a good bibliography to which the reader may refer for more detailed information in these fields.

The latter part of the volume is devoted to the clinical application of these graphic methods in studying various disease states, including rheumatic heart disease, coronary artery disease, myocardial infarction, diseases of the pericardium, etc. In this section of the book, the author points out which of the various means of recording cardiac activity provide information deemed helpful in studying these disease entities. Under the discussion of the disease states, it appears that the author has described numerous findings obtained by graphic means of recording which may be helpful in some instances, and which may be diagnostic in a few, but which will be of questionable value under many circumstances.

Much of the information contained in this volume may be of interest to cardiologists and internists. It is highly improbable, however, that workers in these clinical fields will employ more than a few of the methods of graphic recording described by the author. However, those wishing to familiarize themselves with some of these technical methods of study of cardiac activity will find a ready source of information in this volume.

H. H.

MODERN CONCEPTS IN MEDICINE. By Julius Jensen. St. Louis, 1953, The C. V. Mosby Company. Price $11.50.

As the author points out in the opening sentence of his preface, "This book has been written to facilitate the understanding of internal medicine."

It will be recalled that a year ago, in collaboration with Henry W. Noller, Dr. Jensen published his *Introduction to Medical Science*, (The C. V. Mosby Company, St. Louis, 1952), a volume which has been very well received by medical students and physicians throughout the English-speaking world. The present monograph was partly inspired by a meticulous study of the history of medicine, which the author undertook in preparation for the above mentioned book, and partly by recent progress in the field of cybernetics. Against this background, Dr. Jensen now reviews the whole of internal medicine with a special emphasis upon the role of adaptation and maladaptation. He thus attempts to develop a conceptual basis for an integrated, unitary interpretation of the very nature of disease.

After an introductory chapter, in which he outlines his "functional approach to an integrated concept of medicine," he discusses, at some length, the basic biochemical, physiological and pathological processes, which he considers to be of fundamental importance, both in the process of adaptation and in the genesis of disease. Then follow sections on the "Structural Facilities in Support of Adaptive Processes," in which the individual organ-systems and their diseases are described, and "Cybernetics," in which—after a brief description of the principles of cybernetics—the author proceeds to a study of enzymes, vitamins, endocrines, and the nervous system, as integrators of vital processes in health and disease.

Because of the strong, and often very original views expressed by the author, his philosophic interpretations will, no doubt, provoke a great deal of controversy. However, no one will be able to deny that the book is not only imaginative and thought-provoking, but also represents a brief textbook of both biochemistry and medicine in which quite objective and concise synopses of the chief biochemical processes and disease conditions are outlined in an integrated form.

The composition, illustrations, paper, and binding are in line with the high tradition of the publishing company.

H. S.

VISCERAL CIRCULATION. Ciba Foundation Symposium, 1951. John McMichael, Chairman. Boston, 1953, Little, Brown, & Co. Price $6.50.

This little book contains a wealth of information for the student, anatomist, physiologist, and clinical investigator. Presentations by authorities are discussed freely and critically by other investigators. This is the most valuable feature of the symposium. Much of the work is published for the first time, but sufficient background is given to make the material comprehensible. One feels projected at times into the future by the possibilities of some of the ideas expressed.

A. M.

MODERN ELECTROCARDIOGRAPHY. By Eugene Lepeschkin, M.D. Baltimore, 1952, Williams & Wilkins Company. Price $12.00.

This book is a really remarkable piece of work, which has no counterpart in textbooks published in this country. It constitutes a compendium of world literature on the subject of electrocardiography since 1934. A book of this sort is of great usefulness to the electrocardiographer of some experience in that he can find ready reference to almost any phase of the subject he may wish to investigate. Because the book contains such a vast number of references, it makes very difficult reading for the tyro. It is not recommended for the student who wishes a step-by-step presentation of development of theory in this subject.

Dr. Lepeschkin's section on instruments is one of the best obtainable in the current literature and is of special interest to one who wishes to know the operating characteristics and limitations of modern instruments.

The extent of coverage of the author's reading may be illustrated by the following:

One of the artifacts in electrocardiography is written up in the technical bulletin of a commercial company. Correct reference to this obscure article will be found in Dr. Lepeschkin's book.

This book, with its well-arranged bibliography, is recommended as an indispensable reference work for the library of any electrocardiographer.

C. W.

CARDIOGRAPHIC TECHNIQUE. By S. L. Barron and A. Schott. New York, 1952, Grune & Stratton, Inc. Price $5.50.

This volume is a rather elaborate manual of operation for electrocardiographic instruments and for procedures by cardiographic technicians. The anatomic and physiologic background of the electrocardiogram is reviewed. The construction and operation of various types of electrocardiographic instruments are then described. Some of the material may be confusing to American technicians in that the description involves terms such as "valves" and "mains" rather than the usual American phrases. The volume would appear to be of value where more than the usual operating manual for electrocardiographic instruments is desired by a technician.

J. V. W.

Announcements

BLOOD PRESSURE STUDY IN PERSONS 65 AND OVER

The exhaustive investigation of "Blood Pressure" in men and women under 64 years of age was a landmark in the study of the range of this cardiovascular function. It uncovered many fallacies in our previous concepts. A similar investigation into the "Blood Pressure" range of individuals, 65 years and over, has never been undertaken and is long overdue. It is hoped that the medical profession will give their best cooperation to Dr. Master and his associates in this important investigation. An outline of the background and methods of procedure is given below for the information of our readers.

Editor

Dr. Arthur M. Master, New York, Mr. Herbert H. Marks of the Metropolitan Life Insurance Co., New York, and Dr. Harry L. Jaffe, New York, have undertaken a statistical study of the blood pressure in people who are 65 years of age and over. The investigation is sponsored by The New York Heart Association, New York, The Mount Sinai Hospital, New York, and The Metropolitan Life Insurance Company, New York. The American Medical Association has given aid to the project.

Since hypertension is so common and may lead to heart disease, the correct interpretation of blood pressure readings is of great importance, particularly because of the increasing number of people who undergo routine health examinations in the physician's office, in industrial plants, and in public health studies.

Although previous blood pressure studies had indicated that the incidence of hypertension increased with age, the important influence of age by decade and sex on the normal blood pressure was not taken into account. As a result, an arbitrary figure, usually 150/90 mm. Hg, was used as the upper limit of normal for all adults over 40. This resulted in an excessive incidence of hypertension. Therefore, the blood pressure in 74,000 gainfully employed persons up to the age of 64 was studied. The ranges of normal blood pressure for each decade and by sex were published in 1950. The upper limit of normal was higher for each age group than that previously used.

The evaluation of blood pressure in old age has become a major problem because of the growing number of older people in the United States and the paucity of data in these age groups. Millions of Americans are now 65 years of age or older. With the increasing life span, many more millions will be added within several decades. It is essential to know (1) the normal range of blood pressure as well as the lower limit of hypertension, for each age group over 65 for both sexes, (2) whether the blood pressure continues to increase with age and to vary with sex in those who are more than 65 years old, (3) whether the blood pressure is related to weight, or (4) to surface area or (5) to height.

The relationship of hypertension to coronary sclerosis and occlusion, cardiac enlargement, valvular disease, calcification of the aorta, electrocardiographic abnormalities, hypercholestermia and diabetes may have to be reinvestigated in people over 65, as was recently done up to that age. It had generally been accepted that an etiologic relationship between hypertension and coronary occlusion exists in both sexes. However, using the limits of normal blood pressure newly established for those under 65, it was shown that such a causal relationship exists only in women; in men, no important relationship between hypertension and coronary occlusion was found. Using the new limits of normal blood pressure, it was also found that enlargement of the heart occurred not uncommonly in men with coronary occlusion when their blood pressure had been normal. It was concluded that coronary artery disease alone could produce cardiac enlargement in men. Women with coronary occlusion, on the contrary, rarely developed cardiac enlargement if their blood pressure was normal. Hypertension, therefore, appeared to be a very important factor in the production of enlargement of the heart in women.

THE QUESTIONNAIRE

BLOOD PRESSURE STUDY (AGES 65 AND OVER)—Under Auspices of New York Heart Association, Inc.—Arthur M. Master, M.D., Director

Patient's initials.....Date of Examination.....
Residence: City or Town.....State.....
Color.....Sex.....Age last birthday.....
Height (s shoes).....Ft.....In. Weight (s shoes or clothing).....Lbs.
Country of birth.....
Work: 1. Employed full time.....☐ 3. Unemployed.....☐
2. Employed part time.....☐ 4. Retired.....☐
Occupation: (usual or previous if retired or unemployed)
1. Farming ☐ 2. Light Manual ☐ 3. Heavy Manual ☐
4. Sales, Clerical, etc. ☐ 5. Professional ☐
6. Executive, official or proprietor ☐ 7. Housewife ☐
Chronic Diseases: Major Diagnosis.....
Other Diagnoses.....
.....

Heart Disease: Yes ☐ No ☐ 1. Mild Angina: Y. ☐ N. ☐ 2. Prev. Angina: Y. ☐ N. ☐ 3. Previous Coronary Occlusion: Yes ☐ No ☐ 4. Hypertensive Ht. Dis.: Y. ☐ No ☐ 5. Rheumatic Ht. Dis.: Mitral: Yes ☐ No ☐ Aortic: Yes ☐ No ☐ 6. Prev. Congestive Failure: Yes ☐ No ☐ Other.....

BLOOD PRESSURE		Initial	10 min. later
How taken? Lying down ☐	Systolic		
	Diastolic—4th phase		
Sitting ☐	Diastolic—5th phase		

Previous maximum blood pressure.....Year.....
Remarks (Use other side if necessary).....
.....
Physician's Name.....
Physician's Address.....

Additional copies may be obtained from "Blood Pressure Study", 11 East 100th St., New York 29, N. Y.

For the previous study of people 16 through 64 years of age an excellent source of material was found among the employees of larger industrial concerns. Therefore, for the study of the normal blood pressure in people 65 years of age and older, a pilot study was conducted in 1951 to 1952 in such concerns to determine their availability for data in these age groups. It was found that industry was not a suitable source because (1) relatively few persons 65 or older were employed. Most firms retire their employees at 65. (2) One-half of these companies discharged workers whose blood pressures were beyond an arbitrary, fixed limit which varied from 140/90 to 230/130 mm. Hg. (3) The techniques employed in obtaining blood pressure readings varied tremendously.

Old age homes also proved unsuitable for the study because only scanty blood pressure data were available. It was, therefore, decided to seek the aid of doctors, between the ages of 30 and 60 years, geographically distributed throughout the country, in order to obtain the data required. General practitioners, part-time specialists, i.e., practitioners with a specialty, full-time specialists in internal medicine and cardiovascular diseases, were to be asked to cooperate in the investigation. The number of doctors to be contacted in each state was determined in accordance with the number of its inhabitants over 65.

In the hope of obtaining the cooperation of the American Medical Association in this study, Dr. Frank G. Dickinson, Chief of Medical Economic Research of that organization, was approached. The American Medical Association was able to obtain from its records, the required number of names of physicians in each state. Dr. George Lull, the General Manager, brought this request to the attention of the Board of Trustees of the American Medical Association, who decided to help. Thus were obtained the names of 17,000 physicians to whom printed questionnaires were recently sent.

The questionnaire card was made as simple and as clear as possible. It can easily be completed by the insertion of the figures requested and by check marks in the "yes" and "no" columns. The data on the cards will lend themselves to facile transfer to "punch" cards, and to subsequent statistical analysis on International Business Machines.

Each of the 17,000 physicians was requested to fill out the questionnaires for six newly examined persons: 2 in the 65 to 69 year group, 2 in the 70 to 74 year group, and 2 above the age of 75. It was suggested that one of the latter be 80 years old or over, if possible. The subjects were all to be in fairly good health and not bedridden, although they might have some chronic illness. Those able to do part- or full-time work were particularly desired. If they were well at the time the blood pressure was obtained, people with rheumatic heart disease, chronic coronary disease or hypertension could be included. The most suitable subjects, therefore, were patients coming for routine examination and relatives or friends in the desired age group.

Two blood pressure readings on each subject, 10 minutes apart, were requested, taken in either the reclining position or sitting. The diastolic pressure was to be recorded in both the fourth phase (a definite diminution in the sound) and in the fifth phase (complete disappearance of the sound). If, however, only the fourth or the fifth phase diastolic reading could be obtained, it was to be entered in the appropriate place on the card. The need for accurate readings, to the nearest even digit, was stressed.

The weight of the subject, without shoes or clothing, was to be entered on the questionnaire. Women might wear a slip and stockings, and men their shorts. If the subject was more fully clothed, the estimated weight of the clothes was to be subtracted.

The height of the patient was to be taken with the shoes off. If the patient was wearing shoes, the heel height was to be subtracted from the total height.

The questionnaires were sent by first class mail. Each letter contained a self-addressed, return envelope with postage affixed.

The persons whose blood pressures will be recorded and analyzed are geographically distributed throughout the country, in accordance with the distribution of those who are 65 and older. This is important, since the blood pressure level seems to vary with race and geographic location. Thus, people in tropical and subtropical climates appear to have lower blood pressures, and the incidence of hypertension among them is low.

In earlier studies of gainfully employed persons, between the ages of 16 and 64, the absolute and relative variations in blood pressures, as measured by the standard deviation and the coefficient of variation, were found to increase with weight, particularly after the age of 40 years. The greatest contrast in the mean pressures was found in the older age groups. It will be of interest, then, to study the weight of even older people, i.e., those over 64 years of age.

In analyzing the measurements of such a variable physiologic function as the pressure of the blood, difficulties are encountered because exact figures cannot often be obtained. However, all precautions possible have been taken to round out the blood pressure readings, which will be recorded with care, to the nearest even digit. Physicians in this country usually record readings with terminal zeros and eights, but this was guarded against. In previous studies in each age group of both sexes, the frequency distribution of the blood pressure levels yielded a fairly normal curve. It is hoped to obtain results at least as good, in this newly undertaken research project.

Definitions of "hypertension" among the older age groups will, of course, be established. In addition the incidence of "hypertension" in these age groups according to various old criteria will be computed. It must be emphasized that the new limits of hypertension will have to be correlated with the entire clinical picture.

THE WESTERN SOCIETY FOR CLINICAL RESEARCH will hold its seventh annual meeting, Jan. 29 and 30, 1954, at Portland, Oregon.

Information regarding the meeting may be obtained from Herbert N. Hultgren, M. D., Secretary-Treasurer, Stanford University Hospitals, San Francisco 15, Calif.

THE UNIVERSITY OF MINNESOTA will present a continuation course in FUNDAMENTAL ADVANCES IN INTERNAL MEDICINE FOR INTERNISTS at the Center for Continuation Study next Feb. 15 to 17, 1954. Basic concepts in the fields of infectious disease, gastroenterology, and hematology will be discussed. The faculty will include Dr. Walter Lincoln Palmer, Professor, Department of Medicine, University of Chicago School of Medicine, and Dr. David Shemin, Associate Professor, Department of Biochemistry, Columbia University College of Physicians and Surgeons, New York City. Dr. Shemin will also present the annual Journal-Lancet Lecture on Feb. 16. The course will be presented under the direction of Dr. Cecil J. Watson, Professor and Head, Department of Medicine, University of Minnesota, and the remainder of the faculty will be made up of members of the University of Minnesota Medical School. Housing accommodations at the Center for Continuation Study will be available for physicians registering for the course.